HOSPITAL LIBRARY

Vol. 36 FEBRUARY, 1950 No. 2

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

Editor

BORDEN S. VEEDER
St. Louis

Editorial Board

HARRY BAKWIN	New York
RUSSELL J. BLATTNER	Houston
ALEXIS F. HARTMANN	St. Louis
LEE FORREST HILL	Des Moines
CHARLES F. McKHANN	Cleveland
WALDO E. NELSON	Philadelphia
HENRY G. PONCHER	Chicago
EDWARD B. SHAW	San Francisco

Published by THE C. V. MOSBY COMPANY, 3207 Washington Blvd., St. Louis 3, U.S.A.
Copyright 1950 By The C. V. Mosby Company

Table of Contents on 3rd Cover

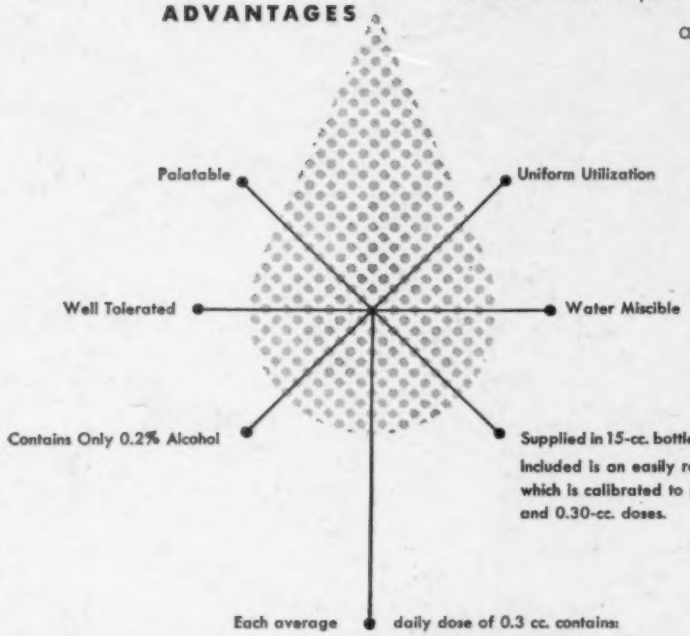
LIBRARY
COLLEGE OF OSTEOPATHIC PHYSICIANS & SURGEONS

'Procebrin'

(Pan-Vitamins, Pediatric, Lilly)

A highly concentrated vitamin preparation especially suitable for routine prophylaxis or therapeutic administration to premature babies, infants, and growing children.

ADVANTAGES

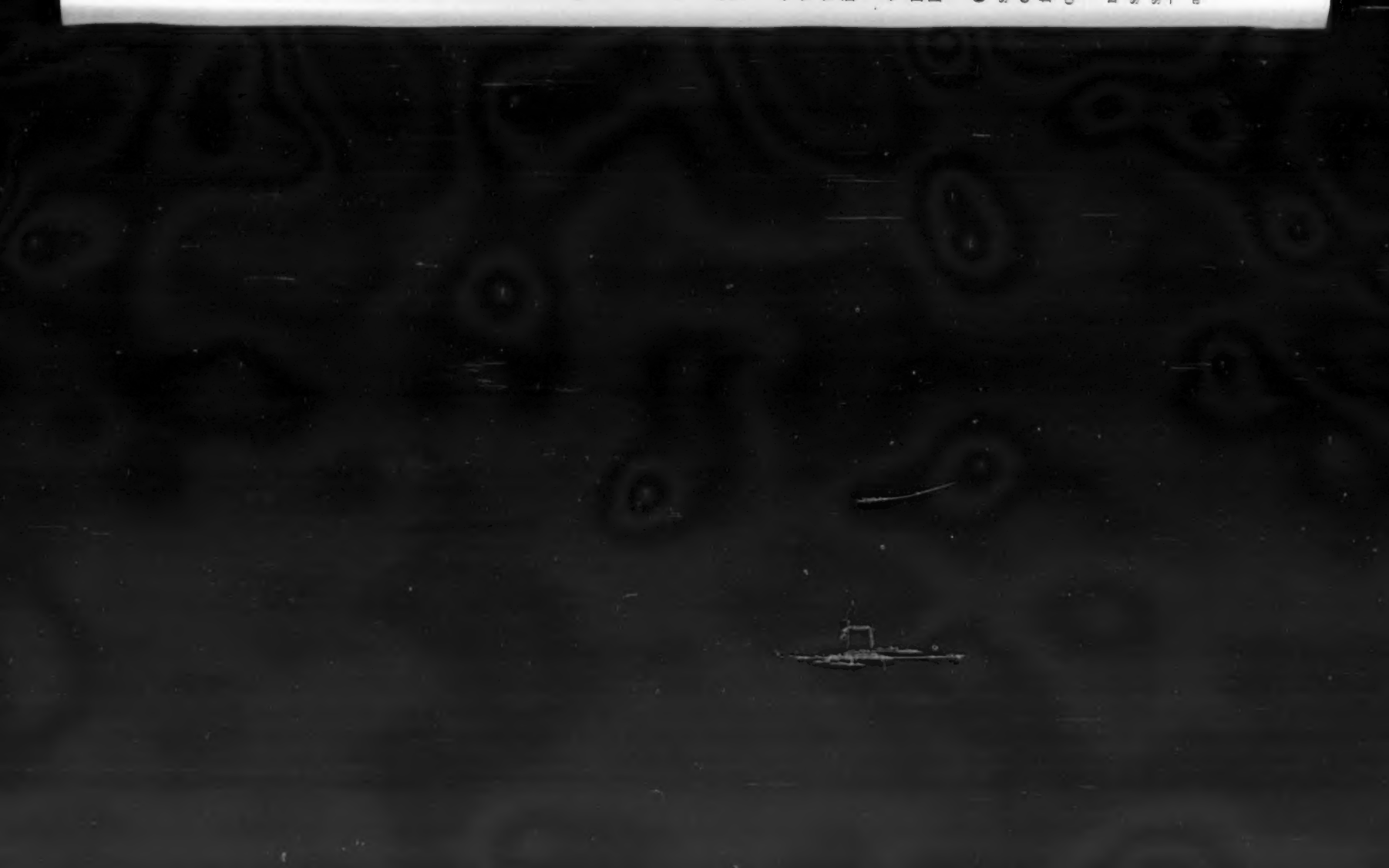

Palatable
Uniform Utilization
Well Tolerated
Water Miscible
Contains Only 0.2% Alcohol
Supplied in 15-cc. bottles.
Included is an easily read dropper which is calibrated to provide 0.15 and 0.30-cc. doses.

Each average daily dose of 0.3 cc. contains:

Thiamin Chloride (Vitamin B_1)	1 mg.
Riboflavin (Vitamin B_2)	0.5 mg.
Pyridoxine (Vitamin B_6) Hydrochloride	0.5 mg.
Pantothenic Acid (as Sodium Pantothenate)	1.5 mg.
Nicotinamide	8 mg.
Ascorbic Acid (Vitamin C)	60 mg.
Vitamin A	3,000 U.S.P. or International units
Vitamin D	800 U.S.P. or International units

ELI LILLY AND COMPANY
INDIANAPOLIS 6, INDIANA, U. S. A.

Vol. 36, No. 2, February, 1950. The Journal of Pediatrics is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: The United States, its Possessions and Pan-American Countries, $10.00 a year; Canada and other foreign Countries, $11.00 a year. Entered as Second-class matter June 29, 1932, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in the U. S. A.



The Journal of Pediatrics

VOL. 36 FEBRUARY, 1950 NO. 2

Original Communications

THE EFFECT OF INHERITED ANTIBODIES ON THE ACTIVE IMMUNIZATION OF INFANTS

LOUIS GREENBERG, M.SC., PH.D., OTTAWA, ONT., AND
DONALD S. FLEMING, M.D., D.P.H., MONTREAL, QUE.

CANADIAN vital statistics show that in the ten-year period from 1938 to 1948 there were 2,365 deaths from diphtheria, 4,007 from pertussis and 191 from tetanus in Canada. It is important to note that of these deaths, 211 (9 per cent) attributed to diphtheria, 2,992 (75 per cent) to pertussis, and 7 (4 per cent) to tetanus, occurred in infants under one year of age. Since diphtheria, pertussis, and tetanus are preventable diseases, a need for more intense immunization programs than already exist is strongly indicated. It is also evident from the above figures that, to be most effective, immunization must be started at a fairly early age—3 or 4 months at the latest.

Until recently it had been generally accepted that infants under 6 months of age did not respond well to active immunization. This belief was based on the contentions that the body processes were not developed to a stage where they could respond properly to antigenic stimuli and that passive antibodies inherited from the mother interfered with active immunization.

Recent studies have tended to discredit this belief and it is now known that very young infants (as young as one month) respond well to vaccinia virus, pertussis vaccine, and tetanus toxoid.[1-6] The response to diphtheria toxoid, however, is less well known.

Many newborn babies inherit diphtheria antitoxin from their mothers and Cooke,[6] Bousfield,[7] and Vahlquist[8] have shown that this interferes with subsequent active immunization. The degree of interference has not as yet been established, and it is the purpose of this study to determine whether this interference is serious enough to discourage immunization in infants under 6 months of age.

Experimental Procedure.—The infants used in this study were chosen at random from healthy children attending the clinics of the Child Health Association of Montreal. Complete records were obtained on 105 of 148 children started in this study. The ages of the latter group were distributed as follows:

From the Laboratory of Hygiene, Department of National Health and Welfare, Ottawa, and the Department of Bacteriology and Immunology, McGill University, Montreal.

AGE IN MONTHS	NUMBER OF CHILDREN
2	2
3	56 (53 per cent)
4	43 (41 per cent)
5	3
Not known	1
Total	105

Prior to inoculation, a sample of blood was taken from each child and the sera were titrated individually for diphtheria antitoxin and, where the supply of serum permitted, for tetanus antitoxin and pertussis agglutinins. Following the blood sampling, each child received a course of three 0.5 c.c. injections, spaced four weeks apart, of an alum-precipitated preparation containing diphtheria toxoid, tetanus toxoid, and pertussis vaccine.* Four weeks after the final inoculation a further blood sample was taken and the sera again titrated for the specific antibodies mentioned above.

RESULTS

Pre-Immunization Sera.—Of 148 sera taken prior to immunization, 47 (32 per cent) were found to have at least 0.002 units of diphtheria antitoxin per milliliter, 4 (3 per cent) at least 0.001 units of tetanus antitoxin and none pertussis agglutinins (Table I).

TABLE I. ANTIBODY LEVELS OF PRE-IMMUNIZATION BLOOD SERA

ANTIBODY	NUMBER OF BLOOD SERA TITRATED	NUMBER OF BLOOD SERA WITH ANTIBODIES
Diphtheria antitoxin (0.002 units or more)	148	47 (32 per cent)
Pertussis agglutinins	148	nil
Tetanus antitoxin (0.001 units or more)	120	4 (3 per cent)

Response to Diphtheria Toxoid.—Of the 105 infants who completed the study, 31 (30 per cent) had more than 0.002 units of diphtheria antitoxin per milliliter in their sera prior to immunization. One month after the final inoculation, the average diphtheria antitoxin titer for the members of this group was 0.51 units per milliliter, whereas the average antitoxin titer for those lacking inherited antibodies was 0.92 units per milliliter (Table II).

TABLE II. DIPHTHERIA ANTITOXIN LEVELS IN INFANTS ONE MONTH AFTER IMMUNIZATION

PRE-INJECTION BLOOD SERA ANTIBODIES	NUMBER OF BLOOD SERA TITRATED	DIPHTHERIA ANTITOXIN TITERS (UNITS)								AVERAGE TITER
		>2.048 <4.096	>1.024 <2.048	>.512 <1.024	>.256 <.512	>.128 <.256	>.064 <.128	>.032 <.064	>.016 <.032	
Absent	74	5	19	23	12	2	5	8	-	0.92
Present	31	0	5	6	5	4	5	5	1	0.51
Total	105	5	24	29	17	6	10	13	1	0.80

*Alum-precipitated Tri-immunol containing 20,000 million *Hemophilus pertussis* organisms, 20 Lf (limit of flocculation) tetanus toxoid, and 50 Lf diphtheria toxoid per ml. Manufactured by Lederle Laboratories, Inc., New York, N. Y. Material from one lot was used throughout the study.

Response to Tetanus Toxoid.—The postinjection tetanus antitoxin levels are shown in Table III. All of the titers were found to be between 0.128 and 8.192 units of tetanus antitoxin per milliliter.

TABLE III. TETANUS ANTITOXIN LEVELS IN INFANTS ONE MONTH AFTER IMMUNIZATION

NUMBER OF BLOOD SERA	TETANUS ANTITOXIN TITER (UNITS)						AVERAGE TITER (UNITS)
	>4.096 <8.192	>2.048 <4.096	>1.024 <2.048	>.512 <1.024	>.256 <.512	>.128 <.256	
105	1	1	16	27	44	16	0.71

Response to Pertussis Vaccine.—The results of agglutination tests on post-immunization sera of ninety infants are presented in Table IV. A wide variation was noted. Four infants had no measurable pertussis agglutinins; the others had titers varying from 1:4 to 1:4,096.

TABLE IV. PERTUSSIS AGGLUTININ LEVELS IN INFANTS ONE MONTH AFTER IMMUNIZATION

NUMBER OF BLOOD SERA	AGGLUTINATION TITERS										
	>1:2048 <1:4096	>1:1024 <1:2048	>1: 512 <1:1024	>1:256 <1:512	>1:128 <1:256	>1: 64 <1:128	>1:32 <1:64	>1:16 <1:32	>1: 8 <1:16	>1:4 <1:8	0
90	1	2	5	10	23	16	17	6	3	3	4

DISCUSSION OF RESULTS

The analyses of 148 preimmunization sera from infants averaging 3 and 4 months of age confirmed the findings in a previous Montreal study.[4] It was observed at that time that since the majority of children of that age lack the specific antibodies, there was need for active immunization against diphtheria, whooping cough, and tetanus. This conclusion is strengthened by Canadian vital statistics which show that over a ten-year period a total of 3,210 deaths due to these three diseases have occurred in infants under one year of age.

Analyses of 105 sera taken one month following immunization showed that infants who possess inherited diphtheria antitoxin did not respond as well to diphtheria toxoid as infants who lacked this inherited antibody. A difference of 45 per cent in antibody production was noted between the groups. Notwithstanding this difference, it is significant that in the group with inherited antibody the lowest titer was at least four times the amount of antitoxin generally accepted as being the Schick-negative or the immune level (0.004 units). Active immunization against diphtheria, therefore, was very satisfactory in every instance.

Barr and co-workers[9] have reported poor results in guinea pigs with passive immunity where the primary stimulus was weak and where there was undue delay between the first and second injection. The potency of the prophylactic used could also greatly affect the resulting response. Wide variation in the immunizing efficiency of toxoids has been reported on several occasions.[10, 11] A recent survey conducted by the Laboratory of Hygiene of diphtheria and tetanus toxoids as sold on the Canadian market has shown wide differences in immunizing efficiency between products prepared by different manufacturers

and also between different lots prepared by the same manufacturer. It is not unusual to find one lot fifty times as potent as another. The significance of this will be appreciated when it is realized that all of the toxoids concerned had met the minimum requirements for potency of both Canada and the United States. Little or no attention appears to have been paid to this aspect of the problem in previous immunization studies. It is to be hoped that the establishment of international standards for diphtheria and tetanus toxoids (now under consideration by World Health Organization) will effect a better control of the potencies of these products. The preparation used in this study when assayed on guinea pigs[11, 12] was found to be fourteen times more effective than the Canadian fluid diphtheria toxoid standard, and approximately 100 times more effective than the Canadian fluid tetanus toxoid standard. The efficiency of the pertussis vaccine was not determined. It is our belief that for both diphtheria and tetanus toxoids, the alum-precipitated product should be at least ten times as potent as the corresponding fluid.

Interference by inherited antibodies with active immunization against diphtheria was reported by Vahlquist,[8] who found that 0.1 units per milliliter or more of inherited antibody interfered greatly with immunization, and recommended that immunization should be delayed until the titer dropped below this level. The titers of sera in this study prior to immunization were all lower than this amount, being between 0.002 and 0.064 units per milliliter. In this series the children with 0.064 units originally gave as good a response as the children with only 0.002 units. The final titer, therefore, did not appear to be affected by the amount of inherited antibody present. There were not, however, sufficient in the series to warrant drawing statistically sound conclusions. Cooke[6] also reported interference by inherited antibody but her results are difficult to assess since 0.03 uints of diphtheria antitoxin (7.5 times the accepted immunity level of 0.004 units) was the lowest level tested for, and there is no way of determining the number who had less than this amount and who, theoretically at least, could have had sufficient antitoxin to render them immune.

The arguments for and against the routine use of tetanus toxoid have been recently presented by Edsall[13, 14] and Press[15] and careful analyses of the data quoted by these authors have brought out the dangers of contracting tetanus from trivial or unrecognized injuries. Their observations support the routine use of tetanus toxoid as a source of protection especially against unrecognized infection. It has been our experience that the public is not prepared to accept immunization against tetanus in infants when an individual course of inoculations is required for this purpose. People are, however, quite willing to have their children immunized against tetanus when the toxoid is given in combination with diphtheria toxoid and pertussis vaccine, and this is a factor that should be carefully considered by all those concerned with the protection of infants from infectious disease.

In this study the response of the infants to tetanus toxoid was extremely satisfactory. While there is some difference of opinion as to what constitutes a protective level of antitoxin against tetanus, the generally accepted level is the

presence of 0.01 units per milliliter of serum. All of the children in the series had more than this amount, and the average titer for the group was 0.71 units.

The statistics given earlier in this paper show that of the three diseases mentioned, pertussis was by far the most frequent cause of death. Over a ten-year period 75 per cent of these deaths occurred in infants under one year of age. Much has been done in the last fifteen years toward the development and improvement of immunizing preparations for pertussis, but these are by no means as effective in controlling whooping cough as toxoid has proved for diphtheria.

The analyses of postimmunization sera from ninety infants showed that all but four had developed pertussis agglutinins (Table IV). None of these children had agglutinins in their sera prior to immunization. The majority of titers were low but since the immune response to pertussis vaccine is reputed to occur from three to four months following immunization, it is only reasonable to assume that higher levels could have been expected at that time. The significance of pertussis agglutinins has not been established, and there has been considerable variation in reported agglutinin levels from different laboratories. For these reasons no attempt is made to evaluate the effect of the pertussis vaccine other than to point out that a response had occurred in eighty-six (96 per cent) of the ninety infants studied.

SUMMARY

1. Active immunization of infants 3 and 4 months of age against diphtheria, whooping cough, and tetanus appears to be a practical and sound procedure.

2. The presence of inherited antibody has some effect in depressing the response to diphtheria toxoid, but in this series it was not great enough to prevent satisfactory immunization in any of the infants. The average diphtheria antitoxin titer of sera taken after immunization from infants with inherited antibody was 0.51 units per milliliter, whereas the average of the group lacking inherited antibody was 0.92 units. The results of this study confirm Vahlquist's[8] and Barr and co-workers'[16] findings that satisfactory immunization of infants can be achieved by using highly potent toxoids.

3. Wide variations exist in the immunizing efficiency of market diphtheria and tetanus toxoids, and the importance of a better control of potency of these products than now exists is discussed.

4. The response to tetanus toxoid was found to be very satisfactory. The average titer for this group was 0.71 units of tetanus antitoxin per milliliter.

5. The results of immunization with pertussis vaccine are less certain since the blood samples were taken before the maximum response was reached. However, 96 per cent of the children did show a response, as indicated by the development of pertussis agglutinins.

The authors would like to express their appreciation to Miss Esther M. Beith, R.N., and to her associates of the Child Health Association of Montreal, who conducted the clinics for this study. Without their co-operation this work would not have been possible.

REFERENCES

1. Stern, C. S.: Simultaneous Immunization Against Smallpox and Diphtheria, Am. J. Pub. Health **25**: 1034, 1935.
2. Miller, J. J.: Immunization Procedures in Pediatrics, J. A. M. A. **134**: 1064, 1947.
3. Lapin, J. H.: Mixed Immunization in Infancy and Childhood, J. PEDIAT. **22**: 439, 1942.
4. Fleming, D. S., Greenberg, L., and Beith, E. M.: The Use of Combined Antigens in the Immunization of Infants, Canad. M. A. J. **59**: 101, 1948.
5. di Sant'Agnese, P. A.: Combined Immunization Against Diphtheria, Tetanus, and Pertussis in Children Over Three Months of Age, Including Evaluation of Effectiveness of Two Immunizing Agents, J. PEDIAT. **31**: 251, 1947.
6. Cooke, J. V.: Antibody Formation in Early Infancy Against Diphtheria and Tetanus Toxoids, J. PEDIAT. **33**: 141, 1948.
7. Bousfield, G.: Diphtheria Prophylaxis in Very Young Infants, Lancet **256**: 1100, 1949.
8. Vahlquist, B.: Response of Infants to Diphtheria Immunization, Lancet **256**: 16, 1949.
9. Barr, M., Glenny, A. T., and Randall, K. J.: Letter to the Editor, Lancet **257**: 36, 1949.
10. Prigge, R.: Die staatliche Prüfung der Diptherieimpfstoffe und ihre experimentellen Grundlagen, Arb. a. d. Staatsinst. f. exper. Therap. **32**: 1, 1935.
11. Greenberg, L., and Roblin, M.: The Biological Assay of Diphtheria Toxoid, J. Immunol. **59**: 221, 1948.
12. Greenberg, L., Gibbard, J., and Morrell, C. A.: The Biological Assay and Control of Tetanus Toxoid, Bull. Health Organ. League of Nations **12**: 365, 1945-1946.
13. Edsall, G.: Medical Progress; Active Immunization, New England J. Med. **235**: 256, 298, 328, 1946.
14. Edsall, G.: Active Immunization, New England J. Med. **241**: 18, 60, 99, 1949.
15. Press, E.: Desirability of the Routine Use of Tetanus Toxoid, New England J. Med. **239**: 50, 1948.
16. Barr, M., Glenny, A. T., and Randall, K. J.: Concentration of Diphtheria Antitoxin in Cord Blood and Rate of Loss in Babies, Lancet **257**: 324, 1949.

HEALTH AND GROWTH OF ALEUT CHILDREN

EDWIN WILDE, M.D.*
ST. PAUL ISLAND, ALASKA

THIS paper is concerned with a study of the general health, growth, and development of Aleut infants and school children on St. Paul Island, Alaska. St. Paul is the largest of a group of barren islands in the Bering Sea known as the Pribilof Islands. These islands are situated between the 56th and 57th degree of north latitude and the 168th and 170th degree of west longitude, about 240 miles north of Dutch Harbor or Unalaska. At the time of their discovery in 1786 by the Russian navigator, Gregory Pribilof, these islands were uninhabited. There was slight evidence that a previous expedition had been ashore on St. Paul Island, but nowhere is there any record of such a visit. These islands are the breeding resort of the Alaska fur seal. The Russians imported from the Aleutian chain of Islands Aleut natives to work for them in the fur seal industry. In regard to the genetic background of these people, there has been a great deal of interbreeding with European races, so that when we refer to them as Aleuts it must be with a great deal of tolerance, for we find among them some with blue eyes and blond hair. These two hereditary traits are recessive and not dominant characteristics. There is little or no doubt that many of these so-called Aleuts are probably seven-eighths white.

Since 1910 St. Paul Island has been under the supervision of the United States Government and the people live under rather rare economic conditions, in that they are wards of the government. All of them are employed by the government and are engaged only in work pertaining to the securing of seal skins. The community is paid a set fee for each fur seal pelt. This is then prorated among the men above 17 years of age, according to their skill in their various occupations. In addition, they receive as part payment for their labor a basic food issue equivalent to 2,765 calories per person per day. This food issue they supplement by hunting and fishing. They have retained their aboriginal hunting and fishing rights so that they may fish and hunt for food irrespective of the season. They also secure added food by purchases from the native canteen. Unlike their brethren to the south of the Aleutian chain who subsist mainly on fish and seal meat, these people live on the white man's diet, which is very high in carbohydrate.

INFANT STUDY

This portion of the study was begun in June, 1945, at which time a well-baby clinic was established. The clinic was held monthly. The attendance was very good. The cooperation of the Aleut mothers was excellent, and they made every effort to carry out instructions in hygiene and infant feeding.

The material for this study was furnished by the Wm. S. Merrell Company, Cincinnati, Ohio.

*Medical Officer, Fish and Wildlife Service, Department of the Interior of the United States of America; and Associate of the Arctic Institute of North America.

In April, 1946, at the instigation of Dr. Roy Lyman Sexton,[2] Washington, D. C., there was added to the diet of these infants a vitamin B complex and iron preparation, Infa-Concemin,* consisting of:

Thiamine hydrochloride (vitamin B_1)	0.8 mg.
Riboflavin (vitamin B_2)	0.8 mg.
Niacinamide	5.0 mg.
Pyridoxine hydrochloride (vitamin B_6)	0.5 mg.
Liver, B complex fraction	67.5 mg.
Rice bran extract	67.5 mg.
Ferrous sulfate	37.5 mg.

Infants up to the age of 2 years were given 20 drops of this syrup each day. This was given as a supplement to their regular diet, which consists, for the most part, of evaporated milk, Karo Syrup, and halibut- or cod-liver oil, whichever was obtainable.

These Aleut infants were breast fed from birth through the first four months of life in 94 per cent of the cases. In only two instances was it necessary to start bottle feeding in the first week of life. In five instances, all in very young mothers, the babies were nursed up to the fifteenth month. After the first four months the breast feeding was gradually discontinued by the mothers, not because of lack of milk, but as a matter of convenience. Peculiarly, the more indolent the mother, the longer she nursed the baby at her breasts. The bottle babies became the fatter babies because of the large amounts of syrup put into the milk in spite of contrary advice.

The usual procedure of dividing the group into two divisions, only one of which would receive the vitamin B complex and iron supplement, was not followed. The Aleut mother is highly sensitive and would feel offended if she did not receive the same medication for her baby as did her neighbor. Therefore, the study of a control group simultaneously was not possible. However, we did have an advantage in having for comparative purposes complete records on a group of infants who during previous years had received essentially the same diet but no vitamin B.

This study continued to May, 1949. At that time the results were evaluated by transposing all of the available data on the fifty-nine infants in this series to a Wetzel Baby Grid.[4-7] The statistics for the tables to follow are all taken from the Wetzel Baby Grid. It would be interesting to the reader if there were sufficient space for the insertion into this article of the individual Wetzel Baby Grid for each infant, but this is impossible.

Table I shows the number of infants in each physique channel. This gives us a rather startling picture of 90 per cent of the infants having a physique of

TABLE I

	PHYSIQUE CHANNEL										TOTAL
	A_3	A_4	A_2	A_2	A_1	M	B_1	B_2	B_3	B_4	
Number	21	13	7	5	7	2	3	1	0	0	59

*Infa-Concemin and Pan-Concemin are trademarks.

medium, normal, or better, with only four out of fifty-nine having a physique in which their weight is too low for their height, and thirty-four out of fifty-nine being or bordering on an obese physique.

Table II shows the number of infants in each auxodrome, or schedule of individual developmental progress. We find thirteen infants in the advanced auxodrome, forty-one in the normal or standard auxodrome, and five in the premature auxodrome, again giving us figures which are comparable to the figures in Table I in that fifty-four of the fifty-nine infants show a normal or advanced physical development.

TABLE II

	AUXODROME			
	ADVANCED	NORMAL OR STANDARD	PREMATURE	TOTAL
Number	13	41	5	59

Table III shows the rate of dentition. This gives us fourteen infants having advanced dentition, thirty-eight infants having an average dentition, and seven having a delayed dentition.

TABLE III

	DENTITION		
	ADVANCED	AVERAGE	DELAYED
Number	14	38	7

A most revealing observation has been the almost complete absence of any serious illness among these infants during their first two years of life. There have been no cases of meningitis, poliomyelitis, rheumatic fever, pneumonia, and arthritis in any of its forms, with the one exception of a case of spastic pylorus. Likewise, there have been no gastrointestinal diseases or appendicitis. The most serious ailments in this group have been traumatic injuries such as are sustained by falls, and even these have been of a minor nature. The most difficult problem has been educating the parents of these infants to the need for cleanliness to prevent a recurrence of diseases such as scabies and impetigo which were prevalent in epidemic proportions on this island until recently.

In July, 1946, a study was conducted by Dr. Russell Payne,[2] of Washington, D. C., on St. Paul Island to determine the specificity of histoplasmin and coccidioidin. Among those in the group tested were five of the infants in this group, all of whom were negative to both of the above and to PPD (purified protein derivative).

TABLE IV

NO. TESTED	HISTOPLASMIN		COCCIDIOIDIN		PPD	
	NEG.	POS.	NEG.	POS.	NEG.	POS.
5	5	0	5	0	5	0

Again in November, 1948, a skin-testing tuberculosis survey was made on St. Paul Island. Of the fifty-nine infants in this group, forty-two showed a

negative reaction, four showed a positive reaction, and thirteen were not brought in by their parents for the test. Of the four who presented a positive reaction, two were siblings whose mother had a history of active tuberculosis which, however, was arrested at the time of the test. The other two came from a family in which there was no known tuberculosis. All of those reacting negatively were then inoculated with BCG vaccine.

TABLE V. REACTION TO PPD, NOV. 2, 1948

POSITIVE	NEGATIVE	NOT TESTED
4	42	13

During this time some interesting side observations have been made. In April, 1947, following the arrival of a ship, St. Paul Island experienced a severe epidemic of influenza of the respiratory type. The ship came from Seattle, Wash., where it is known that the first person with influenza came aboard. At the peak of the epidemic, ninety-five out of 300 people were bedridden with this severe type of influenza. For some strange reason, not one infant became infected. I do not presume to claim any relationship to the vitamin B and iron intake and the increased resistance or immunity of these infants; however, the observation seemed significant.

In March, 1949, this same ship again was the source of an epidemic of influenza. At that time Seattle was having an epidemic of Influenza B[1], an intestinal type of influenza. On this occasion one-third of the infants became afflicted.

During the entire period of four years, there occurred out of sixty-five infant births only two deaths, one in a premature infant weighing 3 pounds who lived four hours and the other in an underweight infant having a partial pyloric stenosis. The latter child died at the age of 4 weeks of malnutrition and neglect.

SCHOOL CHILDREN

In the first section of this report, we considered the health of the infants up to the age of 2 years. Our records on the children from 2 to 5 years of age are rather sketchy, but the records of many of those who are between the ages of 2 and 5 at the present time are incorporated in the foregoing report. This section will be concerned with the health of the children from the ages of 6 to 16. Some of these records cover a period of four years, some of them a period of only one year, but in all cases the developmental progress of the child at the time of the present writing is reported.

During their school life these children receive, in addition to the "three R's" and as a part of their regular curriculum, talks by the public health nurse and a physician in regard to matters of hygiene. All children with minor injuries and ailments are sent to the doctor's office during the morning recess. Absentees are reported to the doctor's office and an immediate check is made to determine whether illness is the cause of absence. A toothbrush drill is held each day in the morning, the brush and powder being supplied by the school, in an attempt to avert dental caries. Each Friday all school children are given

shower baths, at which time either the public health nurse or the doctor makes an inspection for any skin diseases. Each child is given daily a polyvitamin tablet (Pan-Concemin) consisting of:

Vitamin A	5,000 U.S.P. units
Vitamin D	800 U.S.P. units
Thiamine hydrochloride (vitamin B_1)	3.0 mg.
Riboflavin (vitamin B_2)	2.0 mg.
Ascorbic acid (vitamin C)	50.0 mg.
Niacinamide	20.0 mg.
Calcium d-pantothenate	2.0 mg.
Pyridoxine hydrochloride (vitamin B_6)	1.0 mg.

During the school year 1948-49, all the children in the primary room, which comprises the first, second, and third grades, were given 5 mg. of thiamine hydrochloride each day. This was given in an effort to confirm the results of previously reported work on the beneficial effect of thiamine on the mentality of school children. In this series the achievement standards of these children showed no deviation from the standards for the previous year; in other words, their ability did not increase.

The cooperation of the teachers and the children in this effort to maintain the health of the children at a high level was excellent. Twice a year, in April and September, the school children are given a complete physical examination, which includes the traditional measurements of height, weight, and age and other data which are necessary to assess the child's physical developmental progress. Chest measurements and chest expansion were taken to determine whether or not there was any correlation between a very low chest expansion on breathing and the incidence of tuberculosis. None was noted.

These measurements are plotted on the Wetzel Grid for evaluating physical fitness in terms of physique or body build and developmental levels. The grid technique, as developed by Wetzel, has proved very effective in keeping complete records of progress of the health, growth, and development of the school children.

In comparing the physique of these Aleut children according to the grid method, we find (Table VI) that sixty-three out of eighty-nine have a grid rating in channels A_1, M and B_1, which represents a medium type of body build or good physique. Seventeen are rated in the A_2 and A_3 groups, representing a stocky physique, and six fall into the A_4 classification of overly plump or obese. Three are in the B_2 group which is fair in terms of physique, and none of the children are in the B_3 and B_4 groups of borderline or poor physical status.

TABLE VI

PHYSICAL STATUS	CHANNEL	NUMBER
Obese	A_4	6
Stocky, well nourished	A_3	5
	A_2	12
Medium build, good nutrition	A_1	27
	M	21
	B_1	15
Fair	B_2	3
Borderline	B_3	0
Poor	B_4	0

When we consider the auxodromes or the age schedules of development, we find that out of eighty-nine boys and girls, four fall into the 2 per cent group, twenty-four fall into the 15 per cent group, twenty-six fall into the 67 per cent group, twenty-eight fall into the 82 per cent group, and seven fall into the 98 per cent group. Out of the eighty-nine boys and girls, we find thirty-two whose auxodromes are increasing; in other words, whose development is advancing or improving. We find forty-four whose auxodrome is constant and thirteen whose auxodrome is declining instead of increasing.

Some discussion of the home lives of these children is of interest. As stated in the introduction of this report, their economic condition is very unique but at the same time very secure. They are assured of an adequate amount of food, even though some of it may not be to their liking. The Aleut prefers sweets, ham, and hamburger to any other food, but nevertheless an adequate allotment of balanced foodstuff is issued him. To give people foodstuff is one thing; to see that it reaches the table in a palatable, nourishing form is quite another. This problem is no different on St. Paul Island than in any other part of the world. We have very excellent Aleut mothers and very indolent Aleut mothers. It is interesting that both the school teacher and the physician can designate those children who are gaining and those who are losing weight without referring to the charts, because of their intimate knowledge of the home life of each and every child.

In an effort to bolster the morale of these people, we at one time took spot checks among the school children as to what they had had for breakfast at home. These spot checks came up with a surprising answer. On the average, 27 per cent of the children had no breakfast at home; 35 per cent had either milk, or bread and butter, or both; and 38 per cent had a warm breakfast of some sort. This led to a long discussion of the problem as to whether or not a school lunch should be instituted, but the idea was vetoed by those in charge on the grounds that a school lunch was not practical or desirable where no child lived more than 200 yards from the school house. It might be desirable from the standpoint that it would aid the children, but on the other hand it would do nothing to foster a desire on the part of the indolent mother to do anything for her children. The spot checks did stimulate some of the mothers into doing a little bit more for their children.

Another interesting observation which was made was that in comparing the weights and heights on an under- and overweight basis, it was found that the greater percentage of children underweight ranged in age from 6 to 8. As they grew older they were better able to fend for themselves in securing more food at home.

In the matter of illnesses among the school children, the most rampant diseases encountered were scabies and impetigo. However, once these diseases of filth were brought under control, the amount of illness among these school children was negligible. This is borne out by the fact that the rate of attendance in school exceeds 99 per cent. During the past four years, the acute conditions which have been discovered among school children were pulmonary tuberculosis (one case), tuberculosis of the hip (one case) and tuberculosis of the sacroiliac joint (one case). The two cases of tuberculosis in the bones and joints have

been completely arrested, and the patient with pulmonary tuberculosis is in isolation. There have been no severe respiratory or gastrointestinal diseases.

In the matter of immunization, all school children are vaccinated and revaccinated against smallpox. All of them are immunized against typhoid fever, diphtheria, and whooping cough. All of those who have shown a negative reaction to PPD are vaccinated with BCG.

The loss of weight and retarded development in some children can be traced directly to lack of control of the children at home. The Aleut does not discipline his child too well, and as a result the child may sleep at home one night and sleep with a cousin the next night. His hours of going to bed and the amount of sleep he obtains are irregular. During the summer months when the sealing season is in full swing and the village is agog from 2 A.M. until late at night, many of these children get very little sleep. Young boys, especially those 13 or 14 years of age, like to earn a few extra dollars by going out on the killing field and cutting out meat from the seal carcasses. It has been noted that whenever a boy of that age does that type of work during the summer months, there is either a loss of weight or no gain in weight during the six months' period, despite the fact that he receives, along with the sealers, a very high caloric breakfast. It is not enough to compensate for the loss of sleep and overactivity. It has also been observed that during the school year the gain in weight and progress in development are much better among the children than during the summer. Without the Wetzel Grid these observations would have been impossible.

No study of the physical condition of Aleut children would be complete without a detailed reference to tuberculosis. There is one difficulty in making a survey among these children. It is virtually impossible to get an attendance of 100 per cent because of the fact that many of them are constantly visiting relatives either on nearby St. George Island or in one of the villages along the Aleutian chain of islands. For that reason, there must be incorporated in a given survey the number who have not been examined.

In the summer of 1946, of the eighty-nine school children in this series, eighty-three were skin-tested with histoplasmin and all of them gave a negative reaction. Simultaneously they were tested with coccidioidin, and again eighty-three gave a negative reaction. Also at that time they were tested with PPD, with thirty-eight positive reactions and forty-five negative reactions. In November, 1948, as a part of a survey conducted by the United States Public Health Service, these children were again tested with PPD. At this time there were forty-five positive and twenty-eight negative reactions; sixteen either were not available for testing or did not report. Two children who reacted positively to PPD in 1946 reversed their reaction to a negative in 1948. Nine who had reacted negatively in 1946 became positive in 1948.

TABLE VII

	HISTOPLASMIN		COCCIDIOIDIN		PPD	
NOT TESTED	POS.	NEG.	POS.	NEG.	POS.	NEG.
Reactions in 1946						
6	0	83	0	83	38	45
Reactions in 1948						
16					45	28

In January, 1948, a chest x-ray survey was made of these children. The x-rays were taken on St. Paul Island and were read by the tuberculosis specialist of the Alaska Territorial Health Department. Of these children, ten were absent or did not report for x-ray. Activity was reported in one case and was later proved clinically to be active tuberculosis. Two of the plates were suspicious but on complete physical examination tuberculosis was not demonstrated. Sixteen presented increased markings or calcification, or both, and sixty were reported as essentially negative.

TABLE VIII. CHEST X-RAY

ESSENTIALLY NEGATIVE	INCREASED MARKINGS OR CALCIFICATIONS	DOUBTFUL	ACTIVE	NOT TAKEN
60	16	2*	1†	10

*Not proved clinically.
†Proved.

Among these eighty-nine school children there was only one case of cardiac disease. A 16-year-old boy had a systolic murmur heard at the apex which was also heard on the posterior. The heart was not enlarged as the apex was within the midelavicular line. He had no shortness of breath and was exceptionally active. This murmur has been watched for four years and no ill effects have been seen.

In regard to surgery, 37 per cent of the children had their tonsils and adenoids removed. At the present writing three children have hypertrophic tonsils which cause intermittent tonsillitis and should be removed. The only other conditions which required surgery were one simple mastoid, one tuberculosis of the hip, and one tuberculosis of the sacroiliac joint.

In the 1947 epidemic of influenza a very small proportion—16 per cent—were afflicted with influenza. In the 1949 epidemic only 4 per cent were ill enough to remain away from school for more than one day.

We are dealing with a group of children who, because of the close supervision and cooperation of the teachers, public health nurse, and a physician, maintain a high degree of school efficiency as a result of the minimal amount of illness. It would be rather difficult to have such a close-knit organization in any larger community, but in a small community where this type of cooperation can be carried out it is no doubt advantageous to the health of the children.

I am firmly convinced that in addition to the close cooperation of the school authority, nurse, and physician, education of the parents is necessary. The opportunity was offered throughout the past four years of interviewing the parents, not only to stress hygiene but, more important, to impress upon them the fact that they must and should bring their children to the dispensary or medical office at the first signs of symptoms of an illness. Throughout all this time there have been no cases of communicable disease, except influenza, among these children.

SUMMARY

1. The general health, growth, and development of fifty-nine Aleut infants up to 2 years of age and eighty-nine Aleut school children from 6 to 16 years of age have been studied over a four-year period and their progress plotted on the Wetzel grid.

2. A well-baby clinic was established for the study of the infants and clinic was held monthly. Instructions in regard to hygiene and infant feeding and care were given the Aleut mothers. As a supplement to their regular diet the infants received daily 20 drops of Infa-Concemin, a vitamin B and iron preparation. They also were given daily the juice of one orange.

3. Of the fifty-nine infants, fifty-five had a physique of medium, normal, or better, and fifty-four showed a normal or advanced physical development. The general health of these infants appeared to be better than average. Illness among this group was at a minimum.

4. A routine of care for school children was set up which included weekly instructions in health and hygiene, weekly physical checkups, and semiannual physical examinations, and a daily toothbrush drill in the interest of oral hygiene. Each child was given daily as a supplement to his diet one Pan-Concemin tablet. All children were immunized against smallpox, typhoid fever, diphtheria, and whooping cough. Those who showed a negative reaction to PPD were vaccinated with BCG. In 1949 a mass chest x-ray survey was made of these children.

5. In terms of physique, sixty-three of the eighty-nine children had a medium type of body build, seventeen were stocky, and six were overly plump or obese; the remaining three were under par in body build. The age schedule of development of these children showed advancement or improvement in thirty-two, no change in forty-four, and a decline in thirteen. Illness in this group also was at a minimum, as evidenced by the fact that the rate of attendance in school exceeded 99 per cent. There have been no cases of communicable disease, except influenza, among these children, and a comparison of the incidence of this affliction during two epidemics in a two-year period showed a decrease from 16 to 4 per cent. On the basis of the mass chest x-ray survey, only one case of active tuberculosis was reported, although sixteen showed increased markings or calcification. Only four of the eighty-nine children had a serious illness or operation during the four-year period.

CONCLUSIONS

The health of Aleut infants and school children living in the sub-Arctic regions was shown to be somewhat better than average in terms of growth and development, and serious illness was kept at a minimum. Several factors were responsible for this excellent record of good health: (a) daily supplements of a vitamin and iron preparation to the infants and a polyvitamin tablet to the school children, in addition to their regular diet; (b) close supervision and cooperation of the school authority, public health nurse, and physician, together with the keeping of accurate, complete, and detailed records; (c) education of the children and of the parents in matters of nutrition and hygiene.

REFERENCES

1. Collins, H. B., Clark, A. H., and Walker, E. H.: The Aleutian Islands: Their People and Natural History, Washington, D. C., Smithsonian Institution War Background Studies No. 21, 1945.
2. Sexton, R. L., Ewan, J. R., and Payne, R. C.: Determination of the Specificity of Histoplasmin and Coccidioidin as Tested on 356 Aleuts of the Pribilof Islands, J. Allergy 20: 133-135, 1949.
3. Veniaminov, I.: Notes on the Islands of the Unalaska Division, vol. 3, St. Petersburg, 1840, Russian-American Co.
4. Wetzel, Norman C.: Physical Fitness in Terms of Physique Development and Basal Metabolism, J. A. M. A. 116: 1187-1195, 1941.
5. Wetzel, Norman C.: Assessing the Physical Condition of Children: I. Case Demonstration of Failing Growth and the Determination of "Par" by the Grid Method, J. PEDIAT. 22: 82-110, 1943.
6. Wetzel, Norman C.: Assessing the Physical Condition of Children: II. Simple Malnutrition; A Problem of Failing Growth and Development, J. PEDIAT. 22: 208-225, 1943.
7. Wetzel, Norman C.: Assessing the Physical Condition of Children: III. The Components of Physical Status and Physical Progress and Their Evaluation, J. PEDIAT. 22: 329-361, 1943.

THE USE OF PHENURONE IN THE TREATMENT OF EPILEPSY

SAMUEL LIVINGSTON, M.D., AND LASLO KAJDI, M.D.
BALTIMORE, MD.

INTRODUCTION

PHENURONE or phenacetylurea was synthesized by Spielman[1] and its anticonvulsant properties first reported by Everett.[2] Further studies on the pharmacology of Phenurone by Everett and Richards[3] indicated that the drug has a low toxicity, with a duration of anticonvulsant action of three to five hours. Studies in hepatectomized mice indicate that the liver plays a role in the destruction of the drug. Blood studies in dogs receiving Phenurone daily over a period of a year and a half revealed normal red and white counts, and the bone marrow remained essentially normal. The initial clinical trials were reported by Gibbs, Everett, and Richards[4] in a series of ninety cases resistant to other drugs. The results indicated that Phenurone was particularly effective against psychomotor seizures but was also useful in some difficult grand mal and petit mal cases. The drug was usually used in conjunction with other anticonvulsants, and the incidence of toxic side-effects was relatively small. The chief disturbance was an exaggeration of pre-existing personality disorders which in some instances were severe enough to necessitate discontinuing the drug.

Material for Study.—This present study deals with a group of 104 patients of the Epilepsy Clinic of the Johns Hopkins Hospital who were treated with Phenurone. Fifty-six of these patients had been receiving one or more of the usual forms of therapy such as phenobarbital, Dilantin, Mesantoin, Benzedrine Sulfate, or Tridione for at least one year before the Phenurone was started. In each instance the previous medication had proved to be ineffective. Each of these patients was treated with Phenurone plus their previous ineffective medication. The remaining forty-eight patients received only Phenurone.

Seventy-three patients suffered from idiopathic epilepsy and thirty-one from organic (secondary) epilepsy. Eighteen had petit mal spells (simple staring, myoclonic or akinetic); nineteen had grand mal seizures; forty-six had psychomotor seizures; and twenty-one had a combination of grand mal and petit mal seizures.

Seventy-one of the patients ranged in age from 2 to 14 years, and thirty-three from 14 to 48 years.

Duration of Treatment.—All patients were observed for periods ranging from three months to one year. In thirteen patients, the medication was discontinued during the first month of trial because of side reactions. With twenty-

From the Department of Pediatrics, Johns Hopkins University Medical School, the Epilepsy Clinic of the Johns Hopkins Hospital, and Perry Point Veterans Hospital.

one patients the drug was stopped after three months because it proved to be ineffective. The remaining seventy patients received the drug for a period of from six months to one year.

Dosage.—The daily dosage of Phenurone varied from 0.75 Gm. daily to 5 Gm. daily as shown in Table I.

TABLE I. DOSAGE OF PHENURONE

AGE	INITIAL DOSAGE	MAXIMUM DOSAGE
Under six years	0.25 Gm. three times daily	3.0 Gm. daily
Over six years	0.5 Gm. three times daily	5 Gm. daily

Generally, with the younger children (under 6 years of age), the initial dosage of 0.25 Gm. three times daily was increased until satisfactory therapeutic results were obtained. The total daily dose was not permitted to exceed 3 Gm. daily. In the older group, including children over 6 years of age and the adults, the daily dosage varied from 1.5 Gm. daily to 5 Gm. daily. In all instances the medication was administered in three or four doses over the course of the day.

RESULTS

All of the patients followed in this study had suffered with frequent seizures prior to the onset of the Phenurone therapy. In each case the number of seizures during the course of Phenurone therapy was compared with a similar observation period just prior to the starting of the Phenurone.

In evaluating the response to therapy, the following classification was followed:

1. Controlled: no recurrence of seizures during the entire observation period.
2. Markedly improved: number of seizures reduced to less than one-fourth of previous frequency.
3. Improved: number of seizures reduced to between one-half and one-fourth of previous frequency.
4. Failure: number of seizures only very slightly reduced, or the status remained the same, or the seizures became more frequent.

It will be seen in Table II that the drug was most effective in controlling the spells of psychomotor epilepsy of the idiopathic type.

Of the forty-six patients with psychomotor epilepsy treated, twenty-two were controlled; seven were markedly improved; four were improved; and with thirteen the treatment was considered a failure. Of the thirty-three patients benefited, eighteen received Phenurone in combination with their previous ineffective medication, and fifteen received Phenurone alone. Three of these patients have been followed for three months, ten for six months, and twenty for from six months to one year.

Of these forty-six patients, twenty were under 14 years of age, and twenty-six from 14 to 48 years of age. Of the thirty-three benefited, fifteen were under 14 years of age, and eighteen were over 14 years of age.

TABLE II. RESULTS OF PHENURONE TREATMENT WITH RESPECT TO TYPE OF EPILEPSY AND TYPE OF SEIZURE

TYPE OF SEIZURE	NO. OF PATIENTS	CONTROLLED	MARKEDLY IMPROVED	IMPROVED	FAILURE
Idiopathic					
Petit Mal					
(1) simple staring	9	0	0	0	9
(2) akinetic myoclonic	2	0	2	0	0
Grand mal	12	2	3	1	6
Psychomotor	38	20	6	4	8
Mixed (grand mal and petit mal)	12	3	1	1	7
Organic					
Petit mal					
(1) simple staring	1	0	0	0	1
(2) akinetic myoclonic	6	1	1	0	4
Grand mal	7	0	1	0	6
Psychomotor	8	2	1	0	5
Mixed (grand mal and petit mal)	9	1	1	0	7
Total	104	29	16	6	53

The patients with grand mal type of seizures benefited much less. Only two of the nineteen patients treated were relieved of their seizures.

None of the patients with petit mal spells of the simple staring type were helped.

UNTOWARD REACTIONS

Since Phenurone was a new drug at the time this study was started, every precaution was taken to recognize early evidence of untoward reactions. Each patient was seen at two-week intervals during the first six months of therapy, and thereafter they were seen at monthly intervals. White cell counts and hemoglobin determinations were done at each visit, and the urine was examined qualitatively for protein, sugar, and microscopic elements. The pulse and blood pressure were also checked. Serum nonprotein nitrogen and cholesterol determinations were obtained on patients presenting proteinuria.

Untoward reactions were observed in twenty-eight of this group of 104 patients. With thirteen of those manifesting such reactions, the disturbances were sufficiently serious to require withdrawal of the drug. The character and frequency of these disturbances and also the number of patients for whom the drug had to be discontinued because of side reactions are shown in Table III.

TABLE III. SIDE REACTIONS MANIFESTED BY TWENTY-EIGHT* OF 104 PATIENTS WHO WERE TREATED WITH PHENURONE

REACTIONS	NO. OF PATIENTS PRESENTING REACTION	NO. OF PATIENTS IN WHOM DRUG HAD TO BE DISCONTINUED BECAUSE OF REACTION
Proteinuria	11	0
Personality changes	6	6
Skin rash	4*	2*
Headache and feeling of fullness in the head	5	5
Drowsiness	2	0
Hepatitis	1*	1*
Total	28	13

*One patient showed two dissimilar reactions.

No abnormal hematological changes were found. The pulse and blood pressure remained essentially unchanged.

Eleven patients developed proteinuria. None of these patients showed any signs or symptoms of urinary disorders before the Phenurone was administered. The proteinuria was present both in the specimens obtained on arising and in the clinic. It developed within the first two weeks after starting the Phenurone and was transient in nature, as it cleared up in each case after discontinuation of the drug. No red blood cells nor casts were found. In spite of the proteinuria in two of these patients who had been taking Phenurone for eight months, the drug was continued because of the marked control of the seizures. These two patients were hospitalized for detailed study of kidney function, including pyelograms. No impairment of kidney function was demonstrated. The drug was discontinued in the remaining nine patients because it proved to be an ineffective anticonvulsant.

Personality changes were observed in six patients. None of these patients presented significant personality changes before Phenurone was started. These changes developed during the first week of treatment. There was no relationship to dosage. These personality changes consisted of overactivity, marked restlessness, insomnia, constant and often incoherent conversation. The changes were so marked in one patient, an 8-year-old boy, that he was referred to the psychiatric clinic. He became extremely restless, slept very little, remained out late at night, and paid no attention to his parents or teachers. He was belligerent and destructive. His symptoms were so severe that institutionalization was seriously considered. His symptoms, however, diminished promptly after the drug was discontinued and cleared completely in about three or four weeks. It was also necessary to discontinue the drug in the other five patients who presented personality changes.

Skin rashes occurred in four patients. In two patients the rash was generalized maculopapular, and in the other two it was scarlatiniform. The rash occurred during the first two weeks of treatment except with one patient on whom it appeared after four weeks. In this latter case the rash was accompanied by a temperature of 101.4° F. and hepatitis (this case is described in more detail below). In each case the drug was discontinued until the rash had completely disappeared and then was readministered to all of the patients, except to the one who manifested evidence of hepatitis. The rash reoccurred in one of the patients for the second time and the drug was therefore permanently discontinued in this patient.

Five patients complained of severe generalized headache with an associated feeling of "fullness in the head." These symptoms occurred in each patient following the administration of the first or second dose of the drug. The headache was so severe that it was necessary to discontinue the drug in each case. Each patient was tried on the drug for the second time, and in each instance the same symptoms reappeared.

Two patients complained of marked drowsiness after they had taken the drug for one week. The clinical improvement was so good that both patients were anxious to continue the drug in spite of the drowsiness. In each case the drowsiness disappeared in about one month.

One patient presented symptoms of a toxic hepatitis. This patient was a 9-year-old Negro boy who broke out with a scarlatiniform rash about four weeks after the Phenurone was started. His temperature was 101.4° F., and his liver was enlarged to about four fingerbreaths below the costal margin. Several days after the appearance of the rash he developed jaundice. Laboratory examinations at this time revealed a four plus cephalin-cholesterol flocculation test, thymol turbidity of 10.9, alkaline phosphatase level of 27.2 Bodansky units, and a serum bilirubin of 2.0 mg. The fever and the rash disappeared three days after the drug was discontinued. In about one month the liver returned to its normal size, and all of the liver function tests were normal. It is possible that the hepatitis was due to some concurrent infectious process. However, since there was an associated scarlatiniform rash, and also since Gibbs reported a case of jaundice in the group of patients treated by him, this case is being considered as one of hepatitis caused by Phenurone.

COMMENT

According to our knowledge, Gibbs' paper is the only report in the literature dealing with the clinical use of Phenurone. His results were based on an observation period of from one to six months. Our observation period was also short, varying from three months to one year. Both Gibbs' and our patients were previously treated with other drugs without benefit.

Gibbs reported that the seizures of 50 per cent of his patients were either completely controlled or they were greatly benefited. We observed similar improvement in 43 per cent. He stated that "the action of the drug seemed to be equal against the three major types of seizures." In our series 63 per cent of the patients who suffered with psychomotor seizures were greatly improved; whereas, only 31 per cent of the patients with grand mal seizures and 22 per cent of those with minor seizures (petit mal) were greatly benefited. Patients with so-called idiopathic epilepsy responded more favorably than those with organic (secondary) epilepsy since 51 per cent of the former and only 26 per cent of the latter group were markedly benefited.

It is generally known that the psychomotor type of seizure is the least likely to respond favorably to the drugs available at the present time. Both Dilantin and Mesantoin have been the drugs of choice. The results of this study and also those of Gibbs' indicate that Phenurone is much superior to that of Dilantin and Mesantoin in controlling psychomotor seizures. It is of interest to note that all three of these drugs are chemically related to each other.

Since the total number of patients observed by Gibbs and by us is only about 200, it is not unlikely that other workers will find side reactions other than those reported in this study. While Gibbs found urinary changes in only two patients, proteinuria was observed in eleven of our patients. None of these patients revealed blood or casts in the urine as reported by Gibbs. In the course of the administration of the drug, Gibbs reported that one patient developed jaundice. We also observed one patient who presented clinical and laboratory evidence of toxic hepatitis.

We agree with Gibbs that personality changes were the most distressing of the untoward reactions. He observed these marked personality changes only in patients who had pre-existing personality difficulties. The six patients who presented personality changes in this study did not show evidence of personality disorders before starting the Phenurone.

SUMMARY

1. One hundred four patients with epilepsy were treated with Phenurone. Forty-five, or 43 per cent, were either completely controlled or markedly improved.

2. Twenty-eight patients, or 27 per cent, developed untoward reactions while taking Phenurone. It was necessary to discontinue the Phenurone in thirteen of these patients.

3. Personality changes were the most distressing side reactions observed.

4. Toxic hepatitis was encountered in one case.

REFERENCES

1. Spielman, M. A., Geiszler, A. O., and Close, W. J.: Anticonvulsant Drugs; II. Some Acylureas, J. Am. Chem. Soc. 70: 4189, 1948.
2. Everett, G. M.: Pharmacological Evaluation of Anticonvulsant Drugs, Presented before American Branch, International League Against Epilepsy, June 13-14, 1948.
3. Everett, G. M., and Richards, R. K.: Pharmacological Studies of Phenacetylurea (Phenurone) An Anticonvulsant Drug, Proc. Fed. Am. Soc. Exper. Biol. 8: 289, 1949.
4. Gibbs, F. A., Everett, G. M., and Richards, R. K.: Phenurone in Epilepsy, Dis. Nerv. Syst. 10: 47-49, 1949.

TONIC-NECK-REFLEX AND SYMMETRO-TONIC BEHAVIOR

Developmental and Clinical Aspects

Arnold Gesell, M.D., and Louise B. Ames, Ph.D.
New Haven, Conn.

ORIENTATION

THE present paper reports further observations on the early development of postural behavior with special reference to its ontogenetic and clinical implications. Posture is here defined as any position assumed by the body as a whole or by its members in order to execute a movement or to maintain an attitude.

Magnus[15, 16] described a tonic-neck response which occurs in a decerebrate animal when its head is turned to an extreme right or left position. The characteristic response consists of: (a) extension of the forelimb on the side toward which the head is turned; and (b) flexion of the opposite forelimb. The reflex occurred in pure form when the labryinths of the laboratory animal had been extirpated. The reflex was accordingly ascribed to proprioceptive impulses arising in the neck from torsion.

Needless to say, this reflex does not occur in such pure form in the intact human infant where it is subject to various directive stimuli. We retain the term tonic-neck-reflex, however, for its descriptive usefulness, and apply it broadly to quiescent and active asymmetric forms of postural behavior which approximate the characteristic tonic-neck-reflex pattern. It will be convenient to refer to this pattern of postural behavior by the abbreviated convention t-n-r. The symmetro-tonic (s-t-r) pattern, in contrast, is characterized by a midposition of the head and symmetrical arm postures (see Figs. 1 and 2).

Both the t-n-r and s-t-r are so basic in the patterning of postural behavior that they figure in many clinical deviations. Magnus demonstrated the t-n-r in idiots and in patients suffering from extrapyramidal lesions. He was unable to induce a t-n-r in some twenty-six normal infants from a few hours to 16 weeks of age, and came to the erroneous conclusion that the t-n-r is a neuropathologic phenomenon. Forcible manipulation of the head had probably induced symmetric startle and resistance responses in the normal infants. When the young infant is left to his own devices he tends to assume a t-n-r attitude spontaneously. In favorable subjects we have elicited in alternation a left and right t-n-r response simply by moving a stimulus back and forth across the field of vision, the infant responding by appropriate head movements. Our studies have shown that the t-n-r is a normal behavior trait of human infancy during the first sixteen weeks of life. By 20 weeks of age it is usually supplanted by s-t-r responses. The t-n-r becomes a pathologic developmental symptom when it persists with undue dominance beyond the age of 6 months. Many neuromotor clinical deviations are based upon a faulty correlation of t-n-r and s-t-r patterns.

Postural reactions of the fetus have been abundantly investigated both in man and lower animals. Especially notable are the studies of Preyer, Minkowski, and Hooker. Hooker[13] has recorded fetal activities by cinema in a series of documented cases. Dusser de Barenne,[3] in a comprehensive summary, describes the various types of labyrinthine and postural mechanisms common to man and animals.

Fig. 1.

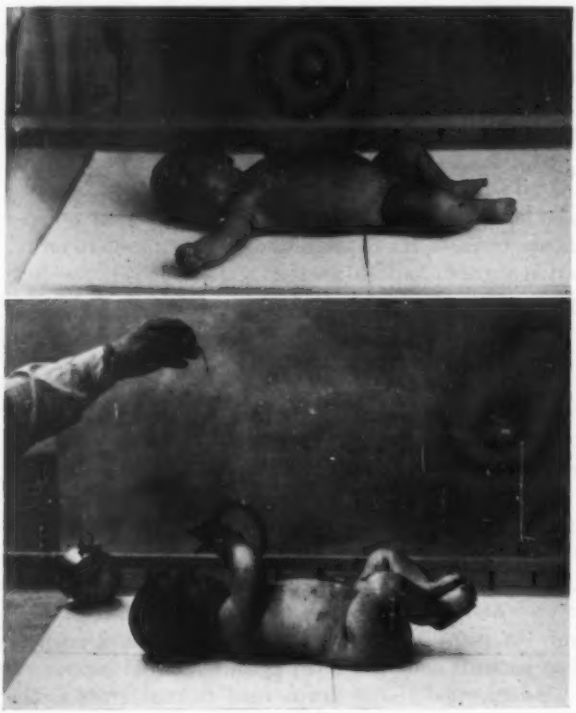


Fig. 2.

Fig. 1.—Spontaneous tonic neck reflex posture of a normal infant age 12 weeks. This attitude was exhibited in the course of a developmental behavior examination.

Fig. 2.—Symmetro-tonic reflex response to the dangling ring situation during a developmental examination of a normal infant aged 20 weeks.

Dr. Randolph Byers[2] has made a detailed, photographically illustrated report of the tonic-neck-reflexes in children, considered from a prognostic standpoint. His report was based on twenty cases of cerebral palsy and noted growth changes in the symptoms over a period of time.

Landis and Hunt[14] have published an extensive report on the Moro and startle reflexes in man. Although their report deals only slightly with developmental aspects, it calls attention to the mechanisms of an important group of symmetric reflex behaviors.

Studies of the Yale Clinic of Child Development have been concerned with the late fetal and early postfetal phases of behavior development. Gesell and Amatruda made a total of eighty periodic observations of the behavior patterning of a group of fetal infants embracing fetal ages from 28 to 40 weeks. Observations on the postural and associated behavior of twenty-two subjects have been reported in detail elsewhere.[6] These observations demonstrated the presence of t-n-r patterns which underwent progressive development throughout the period of fetal infancy.

A previous survey of the behavior development of full-term infants had shown that the tonic-neck-reflex is a normal and virtually universal characteristic of the first eight weeks of life, and that it is gradually supplemented and replaced by symmetric patterns. The tonic-neck-reflex is not a stereotyped, unalterable entity. It is subject to growth changes which involve the contexts and occasions of response. It presents individual differences as well as maturity differences. Normally, in the course of development, the t-n-r complex must be brought into adequate correlation with symmetro-tonic behavior patterns. The intricacy of these correlations imparts clinical significance to the developmental manifestations observable in early postural behavior. The present study will supply additional data secured through cinemanalysis* and clinical observations.

FETAL MANIFESTATIONS

The prevailing postural habitus of the young fetus is symmetrical. Spontaneous head movements are minimal and the head characteristically is set in a midplane position. Trunk, rump, and limbs tend to react in a generalized manner on facial stimulation. Hooker demonstrated that stroking the oral-nasal region of a surgical fetus 8½ weeks of age with a 100 mg. hair elicited contralateral body flexion and a quick backward movement of both arms. The arms moved symmetrically in unison. Similar stimulation of a fetus 11½ weeks of age likewise caused the arms to move bilaterally backward and caudad, bringing the hands simultaneously toward the midplane. This reaction adumbrates a full-blown symmetrotonic posture such as occurs at a postnatal age of about 16 weeks in the full-term infant.

Whether there is any lateral dominance already present in these early fetal postural responses can only be conjectured. Theoretically, it is perhaps safer to assume that both symmetric and asymmetric nascencies are present, and that the ontogenetic sequences will bring them into shifting but progressively patterned relations of dominance and subordination, in obedience to the developmental principle of reciprocal interweaving. Ordinarily it requires over a year of fetal and post-fetal morphogenesis to establish the fundamental framework for asymmetric and symmetric postural attitudes. During this long period the asymmetric mechanisms are pre-eminent or at least more evident.

Minkowski demonstrated that as early as the third to fifth gestation month (8.5 to 23 cm. crown-rump length) passive turning of the head of the fetus to

*Cinemanalysis is accomplished through frame-by-frame inspection of cinema records using a hand-operated desk viewer.

the right resulted in abduction of the right arm and adduction of the left. This reaction contains the first lineaments of the t-n-r pattern. In viable fetuses of more advanced age, this pattern assumes classic form.

Gesell and Amatruda, in their behavior survey of fetal infancy,* found that eight out of ten infants ranging in fetal age from 28 to 40 weeks, spontaneously exhibited well-defined t-n-r postures. The proprioceptive role of head and neck in the production of these postures was determined by a simple maneuver. The examiner, standing at the infant's feet, contacted both of the infant's arms and pressed them lightly against the sides of the trunk. The trunk was very gently and slowly rolled toward the occiput side until the head also participated in the roll, thus reversing the direction of its aversion. The maneuver was executed without lifting the trunk; the head was not touched. As soon as the head turned, the examiner adjusted the trunk so that it lay flat on the table. The degree of passive trunk rotation necessary to induce head turning was noted. The lag or resistance of the head, whether the head turning was active or passive, the maintenance of the new head position, and the return to a preferred side, all were noted. If the head remained in the new posture, the maneuver was repeated in the opposite direction, to compare the response from right to left with that from left to right.

By way of a supplementary "optional" test the infant's head and shoulders were cupped between the examiner's hands, and the head was gently held exactly in midline (in the sagittal plane of the trunk). The observer then released his hands and observed the head reaction of the infant and its consistency for two or three trials. If the head always turned to the same side, the examiner confirmed the observation by an additional test in which the nonpreferred side was slightly favored to note whether the infant still adopted the preferred side as soon as the head was released.

On the basis of the foregoing and related observations, the following three levels of maturity are distinguishable in the development of the tonic-neck reflex responses.[6, 7]

1. The Early Stage Fetal Infant (28 Weeks to 31 Weeks).—Spontaneous head movements are minimal and barely perceptible. The head rotates through a very small arc and is averted to a preferred side. With passive rotation of the trunk, the head passively assumes and accepts a reversed position, typically after traversing an arc of 80 degrees.

Spontaneous head aversion tends always to induce a movement of the corresponding face-arm. This is a primary component of the t-n-r. The occipital arm, after delay, may slowly drift into flexion, giving the impression of a floating t-n-r reminiscent of a pattern which might well occur prenatally in the liquor amnii. From a position of bilateral symmetry, this t-n-r posture may be attained in about five seconds in the very young subject. Reversed t-n-r attitudes, in which the infant faces the flexed occiput arm are also seen, indicating that the head-arm correlation is not yet firmly established.

In the optional t-n-r test every one of the infants in this group showed a preference to rightward aversion. On prone placement, most of them averted

*A prematurely born infant is specified as a fetal infant up to a post-conception age of 40 weeks.

the head so that it rested on the right cheek. This tendency also showed itself strongly in the midstage and late stage fetal infants, suggesting that prone orientations may be the reverse counterpart of supine orientations.

2. The Midstage Fetal Infant (32 Weeks to 36 Weeks).—Head preference for one side persists. The head is more active and rotates through somewhat larger arcs. With passive rotation of the trunk the head lags up to a certain point because of tonic preference for its initial position. On further rotation of the trunk, the head turns actively to the reverse side and accepts the reverse position. This reaction demonstrates a definite increase of muscular tonicity and a partial integration of head and trunk movements.

The access of tonicity is again shown when the fetal infant is placed prone. He is able to lift his head to a small degree, holding it slightly averted.

3. The Late-Stage Fetal Infant (37 Weeks to 40 Weeks).—Tonus of head, neck, and shoulder girdle is now so strongly consolidated that the infant actively resists attempted alteration of position. On passive rotation, the head and trunk revolved as a cylindrical unit with firm connection at the neck isthmus. If rotation is not completed, he rolls back as a single cylinder. In the optional t-n-r situation he consistently adopts the right aversion; and even when slightly constrained toward the left, he favors the right.

In the free supine position there is a preference for rightward orientation at all three of the foregoing levels. Whereas at an earlier stage, head, face-arm, and occiput arm settled into attitude one by one, they now move together more nearly synchronously and with smoother synergy. From a position of bilateral symmetry, a t-n-r attitude of hand and arms is achieved in as little as 1½ seconds, about the same length of time consumed by the full-term infant 8 to 12 weeks of age.

The young as well as mature fetal infant often spontaneously assumes a t-n-r attitude which is strikingly classic in conformation. He may assume such an attitude even when he is drowsing or asleep. In this respect he differs from the full-term infant, in whom there is a sharper distinction between sleep and wakeness due to the development of a cerebral waking center. In the full-term infant the t-n-r tends to vanish with sleep. On waking it may be resumed with a tonic intentness and it may also be activated in a manner which suggests the maturation of higher controls superimposed upon the more primitive reflex circuits. In time, eyes as well as head and neck enter into the total response.

POST-FETAL GROWTH TRENDS

The early development of postural behavior patterns in a group of 107 normal infants was surveyed by means of developmental examinations at fifteen age levels from 4 to 56 weeks.[10, 11] From twenty-six to forty-nine children were examined at each age. All the infants were well at the time of the examination and were born after full-term gestation. Scrupulous regard was paid to the age factor and, with only rare exceptions, each child was examined within two days of the exact chronologic age by the lunar month calendar.

The growth trends in the patterning of t-n-r and s-t-r behaviors are epitomized by the percentage frequencies shown in the accompanying table (Table I). The table lists pertinent behavior items which were observed at 4, 6, 8, 12,

16, and 20 weeks of age, while the infant lay supine in the examining crib. The course of this spontaneous behavior was described while in progress and was stenographically recorded for a period of three minutes. The examiner was stationed inconspicuously at the rear left corner of the crib. No stimulus was applied.

TABLE I. POSTURAL BEHAVIOR PATTERNS (PERCENTAGE OF CASES SHOWING THE INDICATED PATTERNS)

BEHAVIOR ITEMS	AGES IN WEEKS					
	4	6	8	12	16	20
Spontaneous Supine Situation						
Head predominantly rotated	100	97	93	84	20	0
Head predominantly rotated to same side	72	64	79	69	33	-
Head in midposition only momentarily	44	11	25	15	0	-
Head maintains midposition	53	36	48	62	76	100
Head predominantly in midposition	0	4	7	15	67	-
Rotates head from one side to the other	38	32	29	38	57	-
Arms prominently in t-n-r position	100	97	93	64	30	0
Arms prominantly symmetrical	19	18	21	40	63	-
Arms in windmill motions	25	7	11	8	0	0
Hands predominantly open	0	0	8	28	35	69
Both legs active	69	75	71	80	96	-
One leg independently active	35	54	64	58	24	-
Face leg more active than occiput leg	19	36	39	19	0	0
Dangling Ring Situation						
Regards in midplane	29	61	54	54	86	-
Regards in midplane (long head)	22	25	12	50	83	-
Regards in midplane (round head)	32	75	70	56	88	-
Follows approximately 180 degrees	16	43	46	50	68	-
Approaches with both hands	0	0	0	0	50	76

Later in the examination a red four-inch ring suspended by a string was dangled above the infant's chest and moved laterally across the field of vision. The table includes several pertinent behavior items denoting the postural attitudes and reactions which occurred in the dangling ring situation under the influence of visual stimulus. Momentary regard is characteristic of the 4-, 6-, and 8-week levels. Prolonged regard becomes characteristic at 12 and 16 weeks.

Examination of the accompanying table reveals that 100 per cent of the infants at 4 weeks of age, when observed in the free supine posture, spontaneously maintained the head predominantly averted. It is a remarkable fact that 100 per cent likewise held their arms in characteristic t-n-r attitudes. For the first eight weeks the t-n-r attitudes held strong sway. At 12 weeks the typical t-n-r is less prominent, at 16 weeks it was in transition, and at 20 weeks in eclipse, because by that time 100 per cent of our normative infants maintained the head in midposition. When the head is so held, the symmetrotonic patterns supersede the asymmetric. Typically, the eyes converge upon an object of interest, the arms adduct and flex toward the midplane, the hands contact the objects or engage in mutual fingering. The shift from asymmetric to symmetric postures represents a complex developmental transformation. It is not a process of simple substitution, but involves an intricate interweaving cross-stitching which incorporates both asymmetric and symmetric components in a structure which will increasingly come under voluntary control.

Some infants are more strongly addicted to an asymmetric posture than other infants who rotate the head freely or who assume indifferently a left or right aversion. The factors which determine such individual differences must be complex, and vary from child to child. The shape of the head probably exerts an influence, as indicated by an exploratory study by Amatruda. By inspection and cephalic index measurements, a group of infants at the age of 4 weeks were divided into two groups, namely, round heads and long heads. The infants were followed from the age of 4 weeks to 20 weeks. Remeasurements indicated that there was a tendency for the long heads to lose their longness. The head mobility was determined by the dangling ring test for three age groups: 4 to 7 weeks, 8 to 11 weeks, and 12 to 20 weeks. The results show an interesting trend. The round headed infant is more precocious than the long headed infant in maintaining the midposition and in following the ring. These preliminary observations are mentioned to indicate the complexity of the stimulus factors in the patterning of postural attitudes. The total weight of evidence, however, indicates that strong laterality trends are determined by genetic factors possibly reinforced by intrauterine conditions. Indeed it is tempting to suggest that the t-n-r mechanism serves useful functions not only postnatally but also in the last weeks of gestation and even during parturition.

LEGS, FEET, AND TOES

By definition, a complete t-n-r attitude involves the lower as well as the upper extremities. In the typical t-n-r pattern, shoulder, pelvis, and legs share homolaterally in the heightened extensor tonicity. The face-leg is more active than its opposite, but frequently, both in the fetal and past-fetal period of development, the leg attitudes are bilateral and apparently are not affected by the primary head-arm components of the t-n-r. The legs are less subject to tonically maintained attitudes.

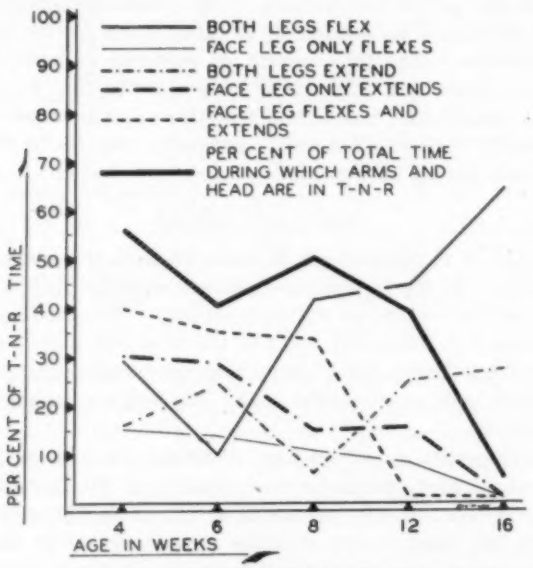
The movement patterns of the legs, therefore, merited special study. This was done by means of a systematic cinemanalysis of film records of the supine behavior of normative full-term infants at 4, 6, 8, 12 and 16 weeks of age. From eight to eleven film records were available at each age. The results of this detailed analysis are summarized in the accompanying graph and table (Graph I, Table II).

The leg behavior most characteristic of t-n-r posturing is active flexion and extension of the face-leg. This behavior predominates at 4 and 6 weeks and is outstanding also at 8 weeks, but does not occur to any appreciable extent thereafter. The face-leg, in its activity, may come to rest in extension or in flexion, resulting in ipsilateral or contralateral extension. (That is, the face-arm and face-leg both may be extended, or the arm may be extended and the leg flexed.) Sustained extension of the face-leg occurs more than flexion, but not by a large margin, and neither is as conspicuous as active flexion and extension of the face-leg. Both legs are flexed, during t-n-r, in a large per cent of cases from 8 weeks on.

The foregoing behavior patterns are quite similar to those which were exhibited by normative supine infants, irrespective of their associated head and arm postures. Unilateral leg flexion and extension is highly characteristic

of the early t-n-r period from 4 to 8 weeks of age. By 12 weeks the legs tend to react bilaterally; they assert this tendency even on the increasingly rare occasions when a frank t-n-r attitude is assumed by head and arms. A more inclusive bilaterality comes into evidence at 20 weeks with the ascendancy of symmetro-tonic postures.

The morphogenetic status of the foot in all these developmental shifts would repay more minute study. Our preliminary observations indicate that toe behavior corresponds in general with leg behavior, regardless of age. At 4 weeks the toes are very active. Flexion, and dorsal extension, often combined with fanning, predominate. The Babinski reflex occurs. At 8 weeks the toes are somewhat less active; flexion is the predominant behavior and continues to be so



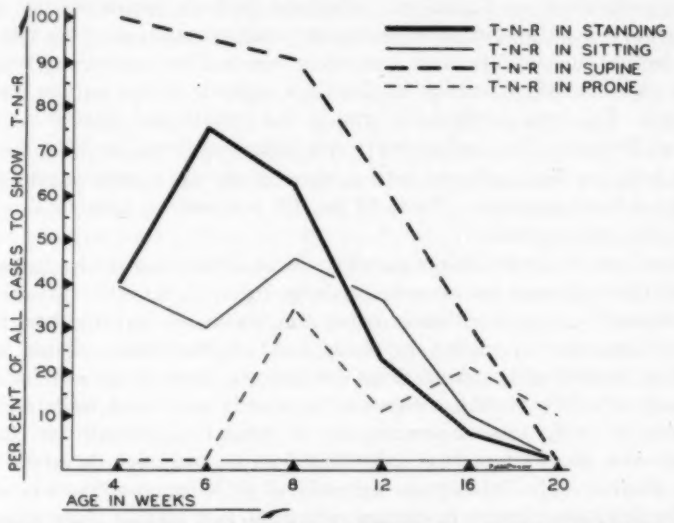
LEG BEHAVIOR IN SUPINE T-N-R
Group averages

Graph I.

TABLE II. LEG BEHAVIORS IN T-N-R OF NORMATIVE CASES (AVERAGES FOR WHOLE GROUP)

AGE (WEEKS)	PERCENTAGE OF WHOLE TIME SPENT IN T-N-R	PERCENTAGE OF T-N-R TIME DURING WHICH				
		LEGS FLEX (%)	LEGS EXTEND (%)	FACE-LEG FLEXES AND EXTENDS (%)	FACE-LEG ONLY EXTENDS (%)	FACE-LEG ONLY FLEXES (%)
4	56	29	15	40	29	15
6	44	9	24	36	28	14
8	51	41	6	33	14	12
12	34	50	25	0	16	9
16	8	65	26	2	2	3
AVERAGES		39	19	23	17	10

at 12 weeks. By 16 weeks, the toes are prevailingly in simple extension. Throughout these age ranges leg behavior influences toe behavior. The tendency is for toes to remain flexed when both legs are flexed and to extend when both legs extend. When there is unilateral leg extension, the toes of the flexed leg tend to remain flexed while the toes of the extended leg remain in simple extension or extend dorsally or Babinski-wise. When one leg alternately flexes and extends (the other leg remaining flexed, as so frequently happens at 4, 6, and 8 weeks) the toes of the flexed leg remain flexed while the toes of the active leg become active. They flex as the leg flexes and extend as it extends.



T-N-R OCCURRING IN VARIOUS POSTURAL ORIENTATIONS

Graph II.

SUPINE, UPRIGHT, AND PRONE MANIFESTATIONS

T-n-r postures are seen to best advantage in the supine infant. The dorsal decubitus reduces the number of deflecting forces and permits the proprioceptive stimuli of the neck to exercise their power. However, these latter stimuli do not cease to operate, at least up to the age of 20 weeks, even when the infant is placed in upright and prone orientations. With the aid of cinemanalysis it was possible to ascertain the relative influence of body postures on the manifestations of the t-n-r attitude. The accompanying graph (Graph II) plots the percentage of cases who exhibited a t-n-r pattern in supported sitting and standing and in prone and supine situations, at 4, 6, 8, 12, 16, and 20 weeks of age. The percentage values approach zero at 20 weeks with the increase of symmetrotonic postures at that age. The highest frequency occurs in the supine situation at 4 weeks, when 100 per cent of the group display the t-n-r. The supported standing situation at 6 weeks and the supported sitting at 8 weeks yielded 75

per cent and 45 per cent, respectively. These values are only suggestive, but they indicate that even under the distraction of an unwonted postural orientation, the t-n-r pattern emerged. At early ages the prone orientation inhibits or alters the manifestation of the t-n-r; at later ages, however, the t-n-r comes into requisition in active pivoting and creeping.

UNILATERALITY AND BILATERALITY

The asymmetry of the t-n-r raises questions concerning laterality and handedness. Is the asymmetry fortuitous or is it consistently determined? Inasmuch as the behavior examinations of the research group of infants were made under standardized conditions in a relatively uniform spatial setting, it is possible to derive some quantitative deductions from the analysis of the film records. The objective cinema data show that there was marked agreement between the specific right or left laterality of the t-n-r attitude in the supine and sitting situations. This was particularly true at the twelfth and sixteenth weeks and less so at 20 weeks when unilaterality was largely replaced by bilaterality.

In both the fetal and post-fetal subjects there was a definite preference for right-sided head aversion. From 71 to 100 per cent in each fetal age group favored the right aversion.

There are clinically observable individual differences in the intensity and scope of the unilateral preferences shown by full-term infants. In some infants the unilaterality clearly embraces trunk and ipsilateral leg; in others there is a crossed dominance of right-handedness and left-footedness. Since maturity, as well as individuality, affects these dominances, their prognostic import must be considered with caution. However, a clearly expressed unilaterality at a succession of early ages is presumptive of similar unilaterality at later ages. In a previous study[8] data were assembled for nineteen cases, in whom the dominance during early infancy as ascertained by cinemanalysis was compared with the dominance shown in cinema records at 1, 5, and 10 years. In fourteen out of a total of nineteen cases, the right or left face-direction of the t-n-r was definitely predictive of later handedness. In five cases the later handedness was ambiguous or contradictive. There were four cases in which left-handedness was correctly foretold by a predominant left t-n-r in early infancy.

COMMENT

The ontogenesis of tonic-neck-reflex behavior in the human infant exemplifies three of the most important principles of development, namely: the principle of developmental direction, the principle of functional asymmetry, and the principle of reciprocal interweaving.

Ontogenetic organization tends to proceed in a cephalocaudad direction determined by a longitudinal gradient. For this reason, the head, shoulder, and arm components are precocious and prominent in the patterning of tonic-neck-reflex postures. The legs lag but ultimately come into the total action system response.

Although the total action system develops as a unitary whole, there is a recurrent accentuation of unilateral functions. In spite of his bilateral con-

struction, man does not face the world on a frontal plane of symmetry. He generally confronts it at an angle. His aggressions and his escapes are executed obliquely. He develops monolateral aptitudes and preferences in handedness, eyedness, footedness, and other forms of unidexterity. Perfect ambidexterity, if it ever exists, might be an abnormality because effective attentional adjustments require an asymmetric focalization of motor set. The t-n-r mechanism is a striking example of how the principle of functional asymmetry serves the architectonics of the action system. The asymmetric attitude promotes and channelizes visual fixation by the infant on his extended hand. It thus leads to the organization of near-point vision, and in due course to reaching, grasp, manipulation, and eventually to unidextrality. In this sense, both the quiescent and the activated tonic-neck-reflex of the infant are conditions of normal behavior growth.

Ontogenetic organization does not advance on an even front. There is a more or less periodic fluctuation of dominance in counterbalanced functions: flexors versus extensors; right versus left extremities; unilateral versus bilateral segments; ipsilateral versus contralateral; near-and-far ocular fixation; monocular and binocular vision. If such dual opposites matured on an even front with simultaneous uniformity, the cycle of growth would lose much of its intricacy, variety, and adaptability. Nature has adopted a method of cross-stitching or interlacing to bring opposing motor systems and functions into reciprocal relationship. This principle rationalizes many of the variable phenomena of the tonic-neck-reflex. It validates the shifting but progressive relationships between the asymmetric and the symmetro-tonic behavioral patterns. Indeed, the principle of functional asymmetry may be regarded as a special inflection of the principle of reciprocal interweaving and is inseparable therefrom. Bilateral and ipsilateral members must be brought both into parallel and diagonal coordinations. This involves an enormous amount of dove-tailing which is accounted for by the pervasive process of neuromotor interweaving. The principle which underlies the process may be formulated as follows: *The organization of reciprocal relationships between two counterpoised sets of interacting functions is ontogenetically manifested by more or less periodic shifting ascendancies of the component functions with progressive integration and modulation of the resultant behavior patterns.*

Viewed in terms of the principle of reciprocal interweaving, the asymmetric and symmetric postural behavior patterns of the human infant assume far-reaching clinical significance. Normality of neuromotor development depends upon lawful timing and balance of the asymmetric and symmetric manifestations. Faulty ontogenetic timing accounts for various forms of transient physiological awkwardness and also for more permanent sensorimotor handicaps. Faulty timing, cerebral injury, and constitutional deviations genetic in origin likewise account for mixed and poorly defined dominances which come to ultimate expression in visual inadequacies, reading and speech disabilities, and neurological symptoms. For all these reasons tonic-neck-reflex and correlated symmetrotonic phenomena are entitled to continuing investigation and to routine clinical scrutiny.

REFERENCES

1. Ames, Louise B.: Supine Leg and Foot Postures in the Human Infant in the First Year of Life, J. genet. Psychol. 61: 87-107, 1942.
2. Byers, Randolph K.: Tonic Neck Reflexes in Children, Am. J. Dis. Child. 55: 696-742, 1938.
3. Dusser de Barenne, J. G.: The Labyrinthine and Postural Mechanisms, Chapter in Handbook of General Experimental Psychology, ed. by Murchison. Worcester, 1934, Clark University Press, pages 204-248.
4. Gesell, Arnold: The Tonic Neck Reflex in the Human Infant, J. PEDIAT. 13: 455-464, 1938.
5. Gesell, Arnold: Reciprocal Neuromotor Interweaving: a Principle of Development Evidenced in the Patterning of Infant Behavior, J. Comp. Neurol. 70: 161-180, 1939.
6. Gesell, Arnold (in collaboration with Amatruda, Catherine S.) The Embryology of Behavior: The Beginnings of the Human Mind, New York, 1945, Harper & Brothers, p. xix, p. 289.
7. Gesell, Arnold, and Amatruda, Catherine S.: Developmental Diagnosis: Normal and Abnormal Child Development, ed. 2 revised, New York, 1947, Paul B. Hoeber, Inc., p. xvi, p. 496.
8. Gesell, Arnold, and Ames, Louise B.: The Development of Handedness, J. genet. Psychol. 70: 155-175, 1947.
9. Gesell, Arnold, and Halverson, Henry M.: The Daily Maturation of Infant Behavior; A Cinema Study of Postures, Movements, and Laterality, J. genet. Psychol. 61: 3-32, 1942.
10. Gesell, Arnold, and Thompson, Helen: Infant Behavior: Its Genesis and Growth, New York, 1934, McGraw-Hill Book Company, Inc., p. viii, p. 343.
11. Gesell, Arnold, and Thompson, Helen: Psychology of Early Growth, New York, 1938, The Macmillan Company, p. ix, p. 290.
12. Giesecke, Minnie: The Genesis of Hand Preference, Monog. Soc. Res. Child Development, 1: 5, 1936., p. vii, p. 102.
13. Hooker, Davenport: Reflex Activities in the Human Fetus. Chapter 2 in Barker, Kounin, and Wright, ed.: Child Behavior and Development, New York, 1943, McGraw-Hill Book Company, p. 652.
14. Landis, Carney, and Hunt, William A.: The Startle Pattern, New York, 1939, Farrar & Rhinehart, p. xiii, p. 168.
15. Magnus, R.: Korperstellung, Berlin, 1924, Julius Springer, p. xii, p. 740.
16. Magnus, R.: Animal Posture, Croonian Lecture, Proc. Roy. Soc., Series B, 98, no. B690, 339-353.
17. Minkowski, M.: Neurobiologische Studien am menschlichen foetus. Abderhaldens Handbuch d. biologischen Arbeitsmethoden, Lief, 253, S. 511-618, 1928.

BLOOD SUGAR VALUES IN PREMATURE INFANTS

MILDRED A. NORVAL, M.D.*
ROCHESTER, MINN.

ALTHOUGH investigations of the level of sugar in the blood of premature infants have been made, the knowledge concerning the accepted range of values during the first two weeks of life is still fragmentary. The purposes of the present investigation were (1) to determine the changes in the mean blood sugar level of premature infants during the growth period from birth to the fourteenth day, (2) to determine the variability of the blood sugar level of premature infants and to ascertain whether this variability changes during the growth period, (3) to ascertain the variability which measures the error of the method, and (4) to compare blood sugar determination as made on premature infants who did not have difficulties with those made on two other groups; namely, normal newly born infants and premature infants who did have difficulties during their early days of life.

REVIEW OF LITERATURE

The results reported in previous studies of blood sugar determinations in premature infants have varied widely. This may have been due to the variety of methods, the source of the blood samples, and the length of the fasting period, as well as to the age of the infant. As indicated in Table I, the greatest range was from 27 to 130 mg. per 100 c.c. of blood; the minimal average reported was 31.8 mg. on the first day of life and 67 mg. at a later age, and the maximal average value was 87 mg. Hartmann and Jaudon[12] said that hypoglycemia is a common occurrence in normal and premature infants, but they did not present any data on premature infants.

Although many authors have found a rapid fall in the blood sugar values shortly after birth in normal newly born infants, Hanley and Horn[10] were the only ones to give determinations on premature infants. The average blood sugar determination on three infants was 132 mg. from the umbilical vein and 122 mg. from the umbilical artery at birth, and 68 mg. six hours after.

Schmal[2] and Van Creveld[4] were unable to find any clear relation between the birth weight or length of gestation and the value for blood sugar in premature infants. Dobrynina-Beljackaja[13] found that a decreased birth weight and a shortened gestation were associated with an increased value for blood sugar in premature infants. With the increase in weight and age of the infant, the curve for the blood sugar values decreased, only to rise later.

Haass[7] found the value for fasting sugar generally to be abnormally low in premature infants who had low body temperature. After warming these infants, the values for blood sugar were significantly higher than values ob-

*First Assistant in Pediatrics, Mayo Clinic, Rochester.

TABLE I. VALUES FOR FASTING BLOOD SUGAR OF PREMATURE INFANTS

AUTHOR AND YEAR	INFANTS		HOURS OF FASTING	METHOD	BLOOD SUGAR (MG. PER 100 C.C.)	
	AGE (DAYS)	NUMBER			RANGE	AVERAGE
Heller[1] 1916	1 to 8	4	½ to 3	Bang	65 to 105	87
Schmal[2] 1924	½ to 51	11	4½ to 6	Bang	51 to 81	69
Mazzeo[3] 1929-1930		31			Same as in newborn infant	
Van Creveld[4] 1929	Less than 60	60	4	Hagedorn-Jensen	27 to ?	
Dessylla[5] 1931	12 to 70	10				67
Svensgaard[6] 1931	4 to 8	11	5½	Hagedorn-Jensen		84
Haass[7] 1931	½ to 21	13		Hagedorn-Jensen	31 to 130	70
Fumagalli[8] 1940	10 to 25	22	4	Hagedorn-Jensen	50 to 95	77
Miller and Ross[9] 1940	1	20		Folin-Malmros		31.8
Hanley and Horn[10] 1943	¼	3		Malmros-Folin-Wu		68
Otila[11] 1948	1 to 30	16	5	Crecelius-Seifert		78

tained while the infants were cool. Kugelmass[14] said that daily studies of blood sugar from birth in newly born infants revealed not infrequently that a corresponding subnormal temperature was associated with a low value for sugar.

Van Creveld[4] showed that the level of blood sugar of premature infants during fasting increased during the first weeks of life. He found that low values occasionally existed at the age of 4 months. The blood sugar of premature infants reached normal values at different ages.

Blood sugar determinations have been made by Liebe[15] on eighty-four premature infants with intracranial hemorrhage. The range (26 to 165 mg.) and the mean (80 mg.) for the blood sugar did not differ from the values previously reported for normal premature infants.

PROCEDURE

This paper is based on blood sugar determinations for forty-two premature infants. If any of the infants had clinical manifestations of cyanosis, twitching, or other pathologic signs, they were arbitrarily grouped as those having difficulties and their blood sugar determinations were considered separately. There were thirty-three premature infants free of any pathologic signs during their hospital stay and nine premature infants with difficulties. The latter infants died during their first few days of life. The birth weight varied between 1,430 and 2,280 Gm. for the premature infants without difficulties, and between 890 and 2,120 Gm. for those with difficulties. The mothers of these infants were free from any obvious metabolic disease.

These premature infants were not fed for at least twenty-four hours after birth and a few were not fed for forty-eight hours. Their feedings were then scheduled every two or every three hours. Depending on the respective

schedule, blood samples for the determination of sugar were made two or three hours after the last feeding. These samples were taken daily in the late afternoon for the first seven to fourteen days of life. Blood for the sugar determination by the micromethod was obtained from a skin puncture in the heel of the infant. Two samples of blood were taken, each with a separate pipette for each set of duplicate determinations.

The blood sugar was determined by a modification of Somogyi's micromethod as previously described.[16] Values as low as 10 mg. per 100 c.c. can be reliably determined by this method. This method constitutes an attempt to measure the "true sugar" contained in the blood in contrast to other commonly used methods which determine the amount of reducing substance in the blood.

On four infants serial determinations of blood sugar were made during the first day of life. At birth the determinations were made by the macromethod of Folin and Wu[17] on blood which was obtained from the placental end of the cord. At least 5 c.c. of blood were collected when the cord was cut at birth. On these same infants, blood sugar determinations by the micromethod were then made for most of the four-hour intervals during their first twenty-four hours of life and at forty-eight hours after birth.

VARIABILITY

Variability of the Method.—Examination was made of the duplicate observations for the normal premature infants, to estimate the size of the technical error. The data provided 399 sets of such paired readings which could be used for this purpose. The average value of the difference between the duplicates was 4.4 mg. per 100 c.c. Measured as standard deviation the technical error was 4.2 mg. per 100 c.c.* or 7.0 per cent of the mean value for the blood sugar. This variation is of the same magnitude as that found previously for newly born infants.[16]

Range and Mean Value.—For the entire group of 798 determinations made for the thirty-three normal premature infants, the mean blood sugar value was 60.0 ± 0.56 mg. per 100 c.c. and the variability, measured as the standard deviation, was 15.3 mg. per 100 c.c. (25.5 per cent of the mean). The range of these readings was from 15.0 to 117.0 mg. per 100 c.c.; the low values were unaccompanied by any signs or symptoms of hypoglycemia. Twenty-three infants (69.7 per cent) had their lowest blood sugar value within the first three days of life, but most of these occurred within the first day. During the first week of life, 462 determinations made on thirty-three infants had a mean value of 56.3 ± 0.72 mg. and the standard deviation was 15.4 mg. During the second week of life 336 determinations made on twenty-eight infants had a mean value of 65.1 ± 0.82 mg. and the standard deviation was 15.1 mg.

The range for the premature infants was approximately the same as that previously found for full-term newly born infants.[16] During the first week of life the mean blood sugar value for the premature infants (56.3 ± 0.72 mg.) was 4.7 ± 0.95 mg. lower than that for full-term infants (61.0 ± 0.63 mg.).

*Each pair yields an estimate of the variance based on one degree of freedom and is equal to one-half the squared differences of the two observations. The average of these is an estimate of the variance of the technical error based on 399 degrees of freedom.

Relation to Age.—When the value for blood sugar was examined in relation to the age of the baby (Table II, Fig. 1), it was seen that it rises during the first week of life and then remains at a relatively stationary level during the second week. It exhibited a marked rise from the first to the second day, which was probably due to the fact that most of these infants had one or more feedings during their second day of life. The decreases from the fifth to the sixth and from the eleventh to the thirteenth days are not statistically significant and represent random fluctuations. As judged by the intradaily variability, measured as the standard deviation, there was no clear evidence that the value for blood sugar became stabilized or that its range of fluctuation decreased during this period. The average intradaily variability was 14.7 mg. per 100 c.c. or 24.6 per cent of the mean.

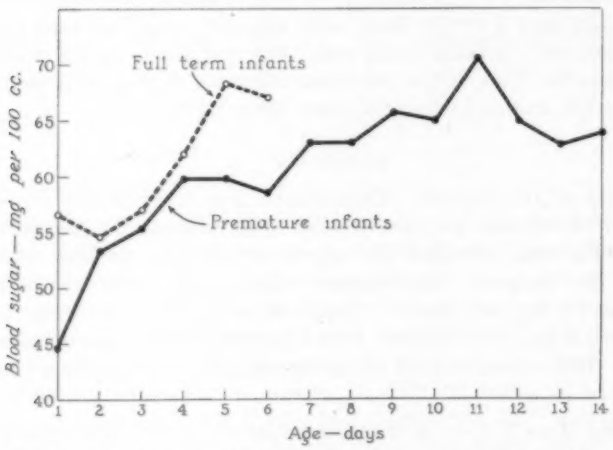


Fig. 1.—Mean values for blood sugar in relation to the age of premature and full-term infants.

TABLE II. BLOOD SUGAR VALUE IN RELATION TO THE AGE OF THE PREMATURE INFANT

DAY OF LIFE	NUMBER OF DETERMINATIONS*	BLOOD SUGAR (MG. PER 100 C.C.)	
		MEAN†	STANDARD DEVIATION
1	66	44.9 ± 1.8	14.7
2	66	53.3 ± 1.6	13.0
3	66	55.3 ± 2.0	16.2
4	66	59.8 ± 1.9	15.5
5	66	59.8 ± 2.0	16.4
6	66	58.5 ± 1.4	11.0
7	66	63.0 ± 1.7	13.8
8	56	63.1 ± 1.9	14.5
9	50	65.7 ± 2.1	14.7
10	48	65.0 ± 2.1	14.4
11	46	70.6 ± 2.9	19.9
12	46	65.0 ± 1.7	11.3
13	46	62.9 ± 2.3	15.4
14	44	63.9 ± 2.0	13.6

*There were two determinations at each observation of an infant.
†The number after the ± is the standard error of the mean.

Relation to Weight, Body Temperature, and Duration of Fast.—When the infants were separated according to birth weight, the values for blood sugar (Fig. 2) were not consistently different one from the other. Even on the first day there was no correlation between the blood sugar value and the birth weight.

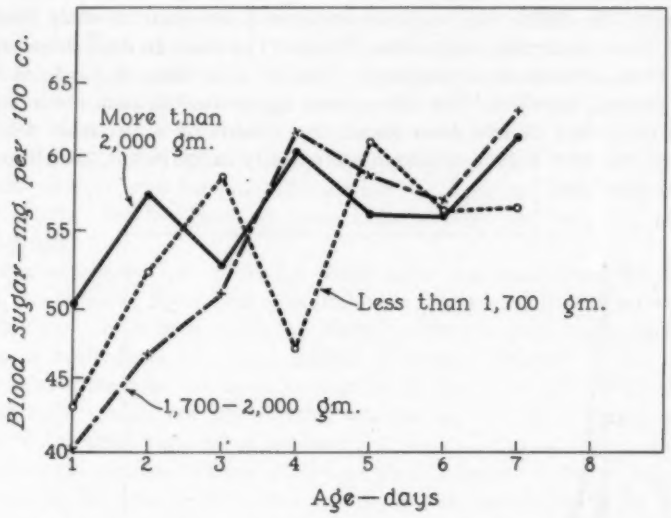


Fig. 2.—Mean values for blood sugar in relation to the age of premature infants. Comparison according to birth weight.

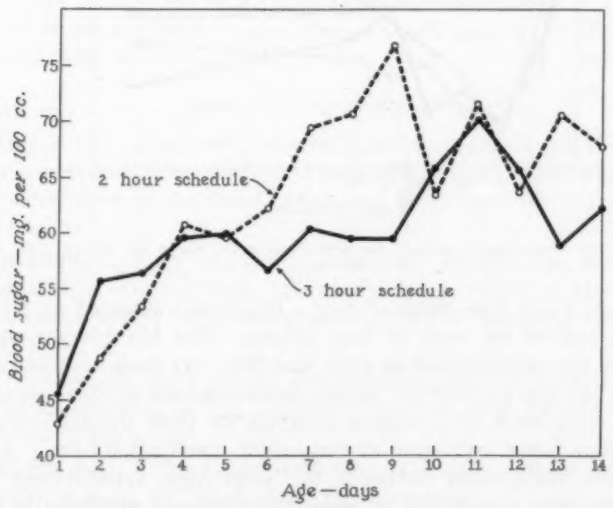


Fig. 3.—Mean values for blood sugar in relation to the age of premature infants. Comparison of a two-hour and three-hour feeding schedule.

Some of the premature infants maintained a very constant temperature throughout their hospital stay while others had an irregular temperature curve; however, none of the temperature curves resembled the blood sugar curves shown in Fig. 1. The temporary declines in blood sugar and the extremely low values were not necessarily associated with low body temperatures or a fall in body temperature.

Eleven of the thirty-three infants were on a two-hour feeding schedule for part or all of their first two weeks of life. The average daily blood sugar values for these infants were compared (Fig. 3) with those for infants on a three-hour feeding schedule. The two curves approximated each other on the fourth and fifth days of life, after which the infants on a two-hour schedule had values which were higher, although statistically insignificant, than those on a three-hour schedule.

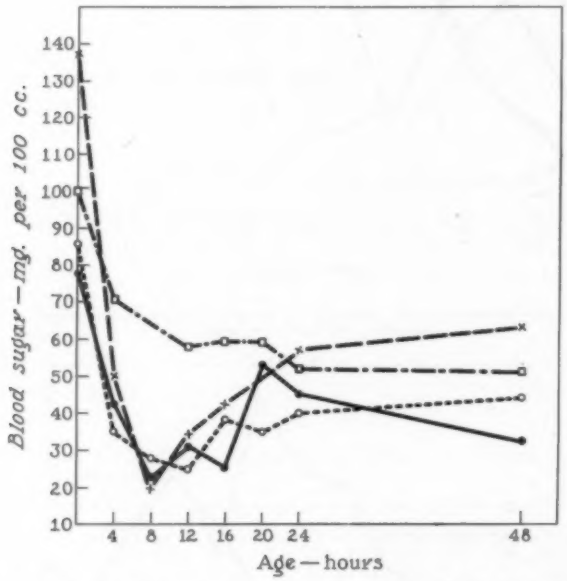


Fig. 4.—Values for blood sugar during the first forty-eight hours of life of four premature infants.

Relation to First Two Days of Life.—Blood was obtained at birth from the placental end of the cord of four infants. The blood sugar values, as determined by the macromethod of Folin and Wu,[17] on these samples varied between 78 and 137 mg. per 100 c.c. Serial determinations of blood sugar by the micromethod were made at four-hour intervals on these infants during their first twenty-four hours and again at forty-eight hours after birth. As shown in Fig. 4, there was a rapid decline in the blood sugar value during the first four hours and then a slow fall to reach the minimum generally in eight or twelve hours after birth. Then there is usually a slight rise until the end of the first twenty-four hours. There was practically no change in the value for

blood sugar during the second twenty-four hours, in spite of the fact that all of these infants received one or more feedings during their second day of life.

Relation to Pathology.—The nine infants who were designated as having difficulties after birth, had birth weights that ranged between 890 and 2,120 Gm. They had grunting, shallow respirations and some were cyanotic, but all died before the third day of life. The clinical and pathologic diagnosis on eight of these infants was prematurity and on the other one it was erythroblastosis fetalis with edema. Five of these infants had values for blood sugar of 22 to 84 mg. per 100 c.c.; these were determined three to twelve hours before death. Four infants had values between 2 (?) and 20 mg.; these died two to fourteen hours after the blood samples were withdrawn. None of the infants had twitching. The infant with the blood sugar of 2 (?) mg. had erythroblastosis fetalis with edema. The sample of blood had been withdrawn three hours before death. None of these infants were fed or given glucose subcutaneously.

The extremely low values for blood sugar may have been due to asphyxia or to the stress of birth (one was undoubtedly associated with edema) or they possibly may have been primary. Selye[18] found hypoglycemia and hypochloremia in individuals who were subject to stress. Others[19-21] have found that starved newborn pigs are more susceptible to the effects of low blood sugar on the first day than they are on the seventh day of life. Symptoms did not occur if the pigs were given glucose.

With the modified Somogyi micromethod it has been shown that premature infants may have values for blood glucose that are as low as 15 mg. per 100 c.c. without symptoms. However, of the nine infants who had difficulties after birth, four had values for blood sugar that were less than 20 mg. This suggests that low values may contribute to or be responsible for a child's difficulties. It seems advisable to give glucose subcutaneously to those premature infants who show any clinical symptoms.

SUMMARY AND CONCLUSIONS

1. Thirty-three premature infants, otherwise normal, were examined for blood sugar content during their first two weeks of life. Microdeterminations, with a modification of the Somogyi method, were used for the evaluation of the blood sugar.

2. In addition, there were nine premature infants who died before the third day of life. Four of them had extremely low levels of blood sugar, but it is not known whether these values were primary or secondary to the infants' condition.

3. The technical error of the determination of the blood sugar, by the method used, measured as the standard deviation, was 4.2 mg. per 100 c.c. (7.0 per cent of the mean).

4. Weight, body temperature, and feeding schedule of the infant did not influence the level of the blood sugar conspicuously.

5. The mean blood sugar value for the entire group was 60.0 ± 0.56 mg. per 100 c.c.; the range was from 15 to 117 mg. per 100 c.c. and the variability,

measured as standard deviation, was 15.3 mg. per 100 c.c. (25.5 per cent of the mean). In the cases in which the low values were obtained, no clinical signs of hypoglycemia were observed. There was no clear evidence that the value for the blood sugar becomes progressively stabilized during this period, as judged by the intradaily standard deviation.

6. The mean value for the blood sugar for these premature infants during the first week of life was lower by 4.7 ± 0.95 mg. per 100 c.c. than the corresponding value previously obtained for full-term infants at birth.

7. During the first day of life serial blood sugar determinations show a rapid decline of values in the first four hours, and then a slower decline to a minimum in eight or twelve hours after birth. There is usually a slight rise in the subsequent twelve or sixteen hours, even when the infants are not fed (Fig. 4).

8. The blood sugar rises progressively in the days following birth, leveling off at about the end of the first week of life (Fig. 1).

I wish to thank Dr. Joseph Berkson, of the Division of Biometry and Medical Statistics for guidance throughout this investigation and for extending the facilities of the Division in the accomplishment of the necessary statistical calculations.

REFERENCES

1. Heller, Fritz: Ztschr. f. Kinderh. **13**: 129, 1916.
2. Schmal, S.: Ztschr. f. Kinderh. **38**: 597, 1924.
3. Mazzeo, A.: Zentralbl. f. d. ges. Kinderh. **23**: 708, 1929-1930.
4. Van Creveld, S.: Am. J. Dis. Child. **38**: 912, 1929.
5. Dessylla, Caterina: Zentralbl. f. d. ges. Kinderh. **25**: 823, 1931.
6. Svensgaard, Elisabeth: Acta paediat. **12**(suppl. 4): 9, 1931.
7. Haass, F.: Ztschr. f. Kinderh. **51**: 400, 1931.
8. Fumagalli, Annamaria: Pediatria. **48**: 610, 1940.
9. Miller, H. C., and Ross, R. A.: J. PEDIAT. **16**: 473, 1940.
10. Hanley, B. J., and Horn, Paula: Am. J. Obst. & Gynec. **46**: 502, 1943.
11. Otila, Eino: Acta paediat. **35**(suppl. 8): 9, 1948.
12. Hartmann, A. F., and Jaudon, J. C.: J. PEDIAT. **11**: 1, 1937.
13. Dobrynina-Beljackaja, N.: Zentralbl. f. d. ges. Kinderh. **25**: 824, 1931.
14. Kugelmass, I. N., Berggren, Ruth E. L., and Cummings, Mildred: Am. J. Dis. Child. **46**: 280, 1933.
15. Liebe, Siegfried: Monatschr. f. Kinderh. **83**: 1, 1940.
16. Norval, Mildred A., Kennedy, R. L. J., and Berkson, Joseph: J. PEDIAT. **34**: 342, 1949.
17. Folin, Otto, and Wu, Hsien: J. Biol. Chem. **41**: 367, 1920.
18. Selye, Hans: J. Allergy **17**: 289, 1946.
19. Graham, Robert, Sampson, Jesse, and Hester, H. R.: Proc. Soc. Exper. Biol. & Med. **47**: 338, 1941.
20. Sampson, Jesse, Hester, H. R., and Graham, Robert: J. Am. Vet. M. A. **100**: 33, 1942.
21. Hanawalt, Vera M., and Sampson, Jesse: Am. J. Vet. Research. **8**: 235, 1947.

PRE-ERUPTIVE NEUROLOGICAL COMPLICATIONS OF THE COMMON CONTAGIOUS DISEASES—RUBELLA, RUBEOLA, ROSEOLA, AND VARICELLA

POPE B. HOLLIDAY, JR., M.D.
NASHVILLE, TENN.

THE occurrence of serous meningitis, encephalitis, and encephalomyelitis as complications of the common eruptive contagious diseases is a well documented fact.[1-40] The diagnosis of such a condition is greatly facilitated by the presence of a characteristic rash or by the history of such a rash in the immediate past. However, the presence of neurological symptoms in the pre-eruptive stage of the disease often constitutes a diagnostic dilemma and may cause considerable anxiety until the eruption appears. Reports of cases with evidence of central nervous system involvement prior to the appearance of the rash have appeared in the literature. However, the fact that such symptoms can occur with any of the common eruptive contagious diseases does not seem to be sufficiently emphasized to result in a high index of suspicion on the part of the practicing physician when confronted with the picture of an acute neurological process of unknown etiology. The experience of the Children's Medical Center during the past twenty years with pre-eruptive encephalitis will be presented with a review of the literature in hope that this information will be of diagnostic assistance. Only the common communicable diseases which have dermatological manifestations, rubeola, rubella, roseola, and varicella, will be considered.

PRE-ERUPTIVE RUBEOLA ENCEPHALITIS

Of the twenty-eight cases mentioned in the literature[1-4, 35, 36, 42, 47] four do not seem sufficiently well established to warrant inclusion in the series. Two patients had encephalitic symptoms ten and fourteen days following measles exposure, did not receive any biological preparation to modify the course of the disease, and did not develop an eruption or Koplik spots.[42] Two other cases were indistinguishable from febrile convulsions as judged from the limited data available.[47]

In the authenticated cases, symptoms and signs have included drowsiness, convulsions, aphasia, hemiplegia, ataxia, diplopia, semi-coma, confusion, and cranial nerve palsy. The interval from the onset of symptoms to the appearance of the eruption varied from one to ten days, averaging four and one-half days. Laboratory data, course of the disease, and prognosis do not differ from that of the familiar posteruptive onset.

Four patients were seen at this hospital from 1928-1948 with diagnosis of pre-eruptive measles encephalitis.

From the Department of Pediatrics, Harvard Medical School, and from the Infants' and Children's Hospitals, The Children's Medical Center, Boston, Mass.

CASE 1.—J. R. was admitted March 12, 1946, and discharged March 26, 1946.

This was the first admission of a 15-month-old white male infant who entered with convulsions of three hours' duration. The past history was irrevalent. The family history revealed that a sibling had developed a measles rash five days previously.

The present illness started two days prior to admission, when the patient developed coryza and cough. On the day of admission he became irritable, drowsy, and feverish. Three hours before arriving at the hospital he had the sudden onset of a generalized tonic-clonic convulsion which persisted in spite of attempts to reduce the fever. No rash had been noted.

Physical examination showed a comatose, slightly cyanotic infant who had rigidity of the trunk and extremities. No convulsive movements were noted. The rectal temperature was 104° F. Over the face and abdomen there was the suggestion of a fine macular rash. Koplik spots were present on the buccal mucosa. The neck was stiff and the deep tendon reflexes were hyperactive bilaterally. There was bilateral sustained ankle clonus. The right chest showed signs of consolidation.

Laboratory data was as follows: urinalysis was normal, the white blood count was 7,800 cells per cubic millimeter, of which 67 per cent were polymorphonuclears, 30 per cent were lymphocytes, and 3 per cent were monocytes, the cerebrospinal fluid on admission was completely normal. Nose and throat cultures grew no pathogenic organisms. A tuberculin test in 1/1,000 dilution was negative. An x-ray of the chest showed a diffuse peribronchial pneumonia, more marked on the right.

Course.—The patient was given 30 c.c. of immune globulin intramuscularly and was begun on parenteral penicillin. No further convulsions occurred, but on the day following admission he had a transient episode of twitching of the muscles of his extremities. On the third hospital day he was still febrile, acutely ill and lethargic, but had become more responsive. On that day a full-blown morbilliform eruption appeared which became hemorrhagic on the face and the extremities, and a positive Babinski's sign bilaterally was noted. The latter was negative on admission. A second lumbar puncture revealed clear fluid under normal pressure with a normal total protein content but with 90 mononuclear cells per cubic millimeter. His subsequent course was one of gradual improvement. Examination on the fourteenth hospital day at the time of discharge revealed no abnormalities. Unfortunately, an appointment for a follow-up examination was not kept.

CASE 2.—V. B. was admitted Aug. 23, 1941, and discharged Sept. 22, 1941.

This was the first admission of a white female 2 years, 11 months old, because of convulsions of seven days' duration. Family history was noncontributory. Past history was completely normal. The patient was delivered by the use of high forceps because of presumed uterine inertia. The neonatal period was without episodes of cyanosis or convulsions. She walked at 14 months and began to talk shortly thereafter.

The present illness began seven days prior to admission when, without previous history of illness, the patient began to have convulsive seizures which persisted until admission. The episodes lasted from a few seconds to several minutes and consisted of screaming, rigidity of the extremities, and urinary incontinence. She was seen in the outpatient department shortly after the onset of her disease, having been referred with the diagnosis of questionable meningitis. Physical examination at that time was completely negative except for a rectal temperature of 100° F. The following day she developed a marked conjunctivitis, slight photophobia, a moderate nasal discharge, slight injection of the pharynx, and many Koplik spots. A white blood count was 8,000 cells per

cubic millimeter. The impression at that time was that she had early measles with convulsions. As her symptoms continued, she was admitted seven days after the onset of her disease. No rash was observed at any time, and there was no known exposure to contagion.

Physical examination revealed a well-developed, well-nourished white female child who had hyperactive deep tendon reflexes and a positive Chvostek sign. The examination was otherwise normal.

Laboratory data was as follows: Urinalysis was normal. The white blood count was 12,800 cells per cubic millimeter, with a differential count of polymorphonuclears 32 per cent, lymphocytes 53 per cent, monocytes 13 per cent, and eosinophils 2 per cent. The cerebrospinal fluid on admission and again on the third hospital day was entirely negative. Blood Hinton and intradermal tuberculin tests were negative. Serum calcium, phosphorus, nonprotein nitrogen, serum protein, heterophil antibody, and blood sedimentation rate were normal. X-rays of the skull, chest, and long bones were normal.

Course.—The differential diagnosis on admission included idiopathic epilepsy, intracranial hemorrhage, tetany, and encephalitis associated with measles. On the day following admission the patient developed marked ataxia of all extremities and equivocal bilateral Babinski signs were apparent. Subsequently her course was characterized by gradual improvement in the ataxia and daily elevations of the temperature to 100° F. for two weeks. During the third week the patient again began to walk. She was discharged home after five weeks apparently entirely recovered except for a very slight ataxia.

She was re-admitted ten months later because of an increase in the ataxia during the preceding six weeks. Neurological examination showed hyperactive right knee and right ankle jerks. In addition, when walking she tended to drag the right leg. Intellectually she seemed more mature than her chronological age. An electroencephalogram and a pneumoencephalogram were normal. A right occipital burr hole revealed no abnormality of the meninges or cortex in that region. The patient has not been seen following this last admission.

CASE 3.—C. F. Y. was admitted Sept. 11, 1933, and discharged Sept. 28, 1933.

This was the first admission of a 2¾-year-old white female because of a hemiparesis of six months' duration. Family history and past history were normal.

The present illness started six months prior to admission, when, three days after a fall out of bed (during which time she was perfectly normal), she had the first of a series of generalized convulsions which lasted for several hours and left the patient with a right hemiplegia, a left facial paralysis, and loss of speech. Three days after the initial convulsion she developed a measles rash. The facial involvement improved in a few weeks, but return of function of the extremities was very slow. During the last few months prior to admission she began to recover her ability to speak.

Physical examination showed a well-developed, well-nourished girl, mentally alert and interested in her surroundings. There was no facial weakness, but a spastic hemiplegia of the right arm and leg was present.

Laboratory studies revealed a normal urine, white blood count, and cerebrospinal fluid.

Course.—Because of the confused history there was some uncertainty as to whether her condition was due to measles encephalitis or to a subdural hematoma subsequent to the fall. Frontal and parietal trephine procedures on the left side revealed no evidence of subdural hematoma, but there was some evidence of cortical atrophy. A ventriculogram showed a normal right ventricle but moderate dilatation of the left ventricle. The presence of a subdural hematoma was thus excluded, although the possibility remains that the cortical atrophy was secondary to traumatic injury.

The patient was seen in the orthopedic and muscle training clinics. At the time of her last visit, seven years after the onset of her hemiparesis, she had completed the fourth grade of school, but still had some spasticity of the right side.

CASE 4.—J. B. was admitted April 29, 1942, and discharged April 30, 1942. This was the first admission of a 6-year-old white boy because of a stiff neck of three days' duration. Family history and past history were irrelevant.

The present illness began four days prior to admission when the patient became feverish. The following morning he awoke screaming with pain in his head and neck, and it was noted that he had some stiffness of the neck with marked increase in pain on flexion of the neck. During the interval preceding admission he vomited several times, had persistent headache, and stiff neck with fever ranging from 100 to 102° F. At times he was restless, disoriented, and hallucinated. Two days prior to hospitalization he developed a slight dry cough and stuffy nose. There was no coma, convulsions, muscle twitching, or known exposure to contagious disease.

Physical examination showed a somewhat drowsy but cooperative white boy who appeared moderately ill. The temperature was 102.2° F. There was a rough, irregular, blotchy, faintly red rash over the face, but none on the trunk. The cervical lymph nodes were moderately enlarged and the neck stiff. A few tiny grayish-white granular lesions were noted on the oral mucous membrane but were not thought to be definite Koplik spots. The pharynx was injected and there was a thick postnasal drip. The neurological examination was normal.

The admission diagnoses were acute cervical adenitis, acute nasopharyngitis, questionable prodromal measles with meningoencephalitis, and questionable virus encephalitis.

The laboratory data showed a normal urine, a hemoglobin of 70 per cent, and a white blood count of 3,200 per cubic millimeter with 72 per cent polymorphonuclears. The cerebrospinal fluid was hazy, under normal pressure, was sterile, and had a normal sugar and protein content. There were 145 white blood cells per cubic millimeter, all mononuclears. The throat culture grew a few Beta-hemolytic streptococci and a moderate number of pneumococci. Intradermal tuberculin test in 1/1,000 dilution was negative.

Course.—The patient's temperature continued at 102° F. and he remained somewhat drowsy but well oriented. There were no convulsions, hallucinations, or vomiting. Late on the evening of admission the rash became more prominent on the face and the lesions in the mouth resembled typical Koplik spots. On the morning of the second day there was a mild, reddish-brown macular rash over the trunk, extremities, and face. At the request of the family the patient was transferred to their local hospital where his course was one of steady improvement, and he was discharged at the expiration of his quarantine period.

A recent interview with the parents and the family physician revealed that the patient is now considered to be a normal boy who is doing well in school, and who has no evidence of personality changes.

Signs and symptoms of a neurological nature which were presented by these patients included convulsions, ataxia, hemiplegia, muscular twitching, positive Babinski's sign, headache, stiff neck, disorientation, drowsiness, and hallucinations. The eruption appeared from three to seven days after the onset of these manifestations, averaging 4.3 days. Of the patients seen in the acute phase, one had a leucocytosis and two had a leucopenia. The cerebrospinal fluid was normal in one, while fluid in the other two showed pleocytosis. On follow-up examinations none of the patients had any intellectual impairment, but one had

some residual ataxia while another had a spastic hemiplegia. In the latter patient (Case 3) the possibility that the hemiplegia was a postconvulsive sequel and that the convulsions were of a febrile nature cannot be excluded, as she was not seen at the hospital until six months after the onset of her disease. The diagnosis of measles encephalitis in the second patient is open to valid criticism. Although the patient had conjunctivitis, coryza, photophobia, and Koplik spots, she did not develop an eruption. The patient in Case 1 had measles encephalitis, but it is impossible to determine if true encephalitic symptoms antedated the eruption. In retrospect, the onset of the disease in this instance cannot be differentiated from febrile seizures.

It is of interest that two patients seen at the hospital and diagnosed as measles encephalitis had received modifying dosages of gamma globulin. Neither, however, ran the true course of attenuated measles. One patient received 0.02 c.c. of gamma globulin per pound of body weight on the sixth day following exposure to measles. Three days later the patient developed prodromal symptoms and, after three more days, thirteen days after exposure, a typical measles rash appeared and the patient was admitted to the hospital following a generalized convulsion, and with a rectal temperature of 102° F. Cerebrospinal fluid was normal on admission. On the fifth hospital day, after the patient had been afebrile for three days, he had an episode of semicoma and generalized muscle twitching lasting for twelve hours. Unfortunately, a second lumbar puncture was a traumatic tap.

The other patient received 0.05 c.c. of gamma globulin per pound of body weight four days after exposure to a sibling with full-blown measles. Six days later, four days prior to admission, the patient developed fever, headache, and malaise. The family pediatrician examined her several times and found no Koplik spots. The symptoms continued, and on the day of admission she had some stiffness of the back and neck. Cerebrospinal fluid showed 150 white blood cells per cubic centimeter, of which 90 per cent were polymorphonuclears, and a total protein of 41.5 mg. per cent. Complement-fixation tests for mumps was negative and her subsequent course was uneventful. Because neither Koplik spots nor morbiliform eruption appeared during her illness, the diagnosis of measles cannot be made with certainty.

PRE-ERUPTIVE RUBELLA ENCEPHALITIS

Fifty-seven cases of posteruptive rubella encephalitis have been mentioned in the literature.[11-20, 37-39, 43, 45] There are three patients reported in whom the occurrence of an exanthem coincided with the appearance of symptoms referable to the nervous system.[12] No case of pre-eruptive encephalitis could be located in the literature or by inquiry.[44] One such patient has been seen at this hospital.

CASE 1.—R. R. was admitted Feb. 10, 1949, and discharged Feb. 24, 1949. This was the first admission of a 2-year-old white female because of convulsions during the preceding thirty-six hours. Family history was significant in that a sibling developed a rash two weeks prior to the onset of the patient's illness. Past history was irrelevant. Development had been normal.

The present illness began three days prior to admission when the patient developed a mild coryza. Thirty-six hours before admission she was found to

have a fever of 102° F. and shortly thereafter she had a generalized convulsion lasting for thirty minutes. For the ensuing six hours she was comatose, but there were lucid intervals and periods of isolated muscle twitching. The patient was given enemata, some fever pills, a pink liquid, and some brown medicine. Her temperature remained elevated and on the day of admission the patient was unresponsive with sudden outbursts of incoordinated motor activity, during which time she would jerk, kick, and throw her arms and legs about. There was no vomiting, known trauma, previous convulsions, or urinary complaints. There was a history of pica as the patient had ingested some wall plaster. In addition to exposure to the sibling there was an epidemic of "measles" in the neighborhood.

Physical examination revealed a well-developed, well-nourished, slightly dehydrated, semicomatose girl, who appeared acutely ill and who had sudden episodes of twitching, kicking, and whining. Rectal temperature was 104° F. She responded only to very painful stimuli, at which time she cried out with a high-pitched scream. Her pupils were dilated, equal, and reacted very sluggishly to light. There were aimless movements of the eyes. On the buccal mucosa and tongue were small abrasions. No Koplik spots were seen. There was hypertonia of all muscles without true spasm and there was no evidence of paralysis. The cranial nerves and deep tendon reflexes were apparently normal. The neck was supple and Kernig sign negative. The remainder of the examination was within normal limits.

Laboratory examination of a catheterized urine specimen revealed a 2 plus albumin and a rare red blood cell and occasional white blood cell per high-power field. Hemoglobin and red blood count were normal. The white blood count was 34,000 per cubic millimeter with a differential of polymorphonuclears 64 per cent, lymphocytes 32 per cent, monocytes 4 per cent. Examination of the cerebrospinal fluid on two occasions showed sterile clear fluid with normal sugar and protein content. Pressure determinations were unsatisfactory due to struggling of the patient. Cell counts showed only 10 and 4 mononuclear cells per cubic millimeter. Tuberculin skin cultures grew no pathogenic organisms. Heterophil antibody and febrile agglutinations were normal. X-rays of the long bones suggested the possibility of a deposition of a heavy metal in the zones of provisional calcification, but a lead determination on a twenty-four-hour urine collection was normal.

Course.—She was given parenteral fluids, penicillin, and sulfadiazine. Rectal paraldehyde was given to control her restlessness. After the first hospital day her course was afebrile, although for the first two days she remained disoriented and had episodes of thrashing about and muscle twitching. On the third day she was greatly improved, attempted to talk, responded to vocal stimuli, was much more alert, and was taking fluids well by mouth. However, she demonstrated a striking ataxia. While sitting up she would weave in a rotary fashion until she finally fell over. Also on the third hospital day she developed a fine, generalized maculopapular eruption which lasted for about eighteen hours. Small posterior occipital nodes were palpated. Subsequently her course was one of continued improvement. Her ataxia gradually decreased. With hydration her nonprotein nitrogen returned to normal and her urinary findings disappeared. The white blood count was 10,000 per cubic millimeter on the fifth hospital day. An electroencephalogram was normal. Psychological appraisal shortly before discharge revealed a child who was quite irritable with short attention spans and who became unsteady when tired. This was a marked change from her activity and disposition prior to her illness. A re-evaluation six months later showed improvement. However, the patient still walked with a wide base and was somewhat irritable and erratic.

An interview with her physician revealed that on the day after the patient entered the hospital a second sibling developed fever and on the following day

a rash appeared. Two days later a second sibling had the same symptoms. It was his opinion that these were cases of rubella and were similar to those he had previously seen in the neighborhood.

This patient had the onset of encephalitic symptoms three and one-half days prior to the eruption. Her pre-eruptive course was that of an acute encephalitis with fever, convulsions, coma, disorganized movements, muscular twitching, and ataxia. There was no doubt that the rash was due to rubella. No Koplik spots were seen. The exanthem had the typical appearance of German measles and was transient in nature. Cases of rubella had been observed in the neighborhood. Three siblings developed a disease resembling rubella. Although the diagnosis of pre-eruptive encephalitis was made prior to the appearance of the rash, steps were taken to rule out lead encephalopathy, infectious mononucleosis, dysentery, uremia, acute bacterial meningitis, and brain tumor. Her cerebrospinal fluid was within normal limits. In contradistinction to the usual case of rubella, this patient had the leucocytosis often seen with the encephalitic complication of the eruptive contagious diseases. Her course was one of improvement, but on discharge and at a six months follow-up she demonstrated personality changes and residual ataxia.

PRE-ERUPTIVE ROSEOLA ENCEPHALITIS

Febrile convulsions are frequently seen prior to the appearance of the exanthem in this disease. However, there are but two cases in the literature reported as pre-eruptive encephalitis. Rosenblum in 1945 cited one patient with pre-eruptive fever and convulsion who appeared in good condition and alert following an initial seizure.[29] Forty-eight hours later a hemiplegia appeared and after another forty-eight hours the rash was noted. The cerebrospinal fluid was normal and the patient made an uncomplicated recovery with disappearance of the hemiplegia. Another patient had fever, vomiting, stiff neck, headache, vertigo, questionable seizures, and semi-coma during a two day period prior to the eruption.[30] Again the cerebrospinal fluid was normal and there were no sequelae. In the report of an epidemic of roseola,[48] one patient was mentioned who developed pyrexia, headache, photophobia, general malaise, rigidity of the neck, and a questionably positive Kernig's sign. The cerebrospinal fluid was normal. Several days later her temperature fell to normal and a rash appeared.

During the past twenty years there have been numerous patients admitted to the Children's Medical Center with roseola. Of this group four patients had evidence of pre-eruptive central nervous system involvement which could be distinguished from febrile convulsions. One other patient who developed signs of meningeal irritation on the day which the rash appeared is included.

CASE 1.—L. S. P. was admitted March 19, 1934, and discharged March 24, 1934.

This was the first admission of a 16-month-old white boy whose chief complaint was athetoid movements of two days' duration. The family history was irrelevant. Past history revealed that the patient was born by full-term, normal delivery with no neonatal distress or previous convulsions. His development had been normal.

The present illness began the day prior to admission when the patient became feverish and had a short period of coma during which time there were athetoid movements of all extremities. Physical examination at that time revealed a temperature of 101° F., a red throat, and some cervical adenopathy. After a similar episode on the day of admission, the patient was hospitalized. Physical examination showed a temperature of 101.4° F., and signs which were unchanged from the previous examination.

Laboratory data revealed a normal urine, hemoglobin, and red blood count. The white blood count was 3,900 per cubic millimeter with 30 per cent polymorphonuclears. Tuberculin test in 1/1,000 dilution and examination of the cerebrospinal fluid were reported as negative.

Course.—The patient was seen by a consultant who felt that the picture was one of encephalitis of infectious origin. No specific medication was given and the temperature returned to normal on the third day. There were no further episodes of athetosis and the patient was discharged home on the fifth hospital day. He was seen the following day, at which time he had developed a rash typical of roseola.

CASE 2.—J. R. was admitted May 20, 1939, and discharged May 23, 1939.

This was the first admission of an 8-month-old white female whose chief complaint was fever of two days' duration. The family history revealed that a maternal cousin had epilepsy and that the maternal grandmother had been institutionalized at 70 years of age because of mental disease. Past history showed that the pregnancy, delivery, and neonatal period were normal.

The present illness began two days before admission when the patient developed a fever of 104.6° F. The fever persisted until admission although no other signs appeared, and it was noted that the patient was not as sick as the degree of pyrexia would lead one to expect.

Physical examination on admission revealed a temperature of 105° F., some palpable posterior cervical glands, and an anterior fontanel which was markedly full and bulging. The remainder of the examination was normal.

Laboratory data was as follows: The urine showed only a few hyaline casts. Hemoglobin was normal. The white blood count was 12,500 per centimeter with a differential of polymorphonuclears 74 per cent and lymphocytes 26 per cent. The cerebrospinal fluid was under increased pressure (no figure given). There were no cells; the sugar was normal; the Pandy was negative; and the culture was sterile. Nose and throat cultures grew no pathogenic organisms. An x-ray of the chest was normal.

Course.—The temperature fell to normal on the second hospital day without therapy, and on the third day a rash characteristic of roseola appeared. The patient was then discharged. She was readmitted in September, 1940, at the age of 2 years because of nine convulsive seizures since the age of 14 months. Interval history revealed that the patient had developed normally, having begun to walk at the age of 17 months and having begun to talk at 2 years of age. However, at 14 months of age she began to have episodes of generalized stiffness of two to three minutes' duration, followed by limpness for two to three hours. There was no associated incontinence or frothing of the mouth. Physical examination on admission was completely negative. Laboratory data included examination of the cerebrospinal fluid, pneumoencephalogram, x-rays of the skull and long bones, and determination of the serum calcium, phosphorus, and phosphatase, all of which were normal. Electroencephalogram showed a diffuse slow wave disturbance with some 3-per-second wave spikes. The impression was petit mal, idiopathic type.

CASE 3.—E. C. was admitted Dec. 17, 1930, and discharged Dec. 23, 1930.

This was the first admission of an 8½-month-old white female because of irritability of two days' duration. Family history and past history were noncontributory.

The present illness began the day before admission with the sudden onset of fever, diarrhea, irritability, and retraction of the neck. Signs of meningeal irritation with bulging of the anterior fontanel were sufficient to warrant a lumbar puncture. Otherwise the examination was negative.

Laboratory data was as follows: The white blood count was reported as "low." The cerebrospinal fluid was said to be normal except for increased pressure, the exact reading not being given.

Course.—The eardrums were incised shortly after admission and a slight serous discharge was obtained. The temperature fell to normal on the second day and a rash appeared which was said to be typical of roseola. The meningeal signs cleared and the patient was discharged home on the seventh hospital day.

CASE 4.—R. W. was admitted Aug. 5, 1945, and discharged Aug. 9, 1945.

This was the first admission of a 13-month-old white male infant because of fever of one day's duration. The family history and past history were irrelevant.

The present illness began three days prior to admission when the patient was noted to be unusually drowsy and irritable. He held his neck rigid and would not turn his head to either side. His mother observed that flexion of his neck caused pain. The following day he was somewhat improved, but on the third day he became more irritable. The family physician found a rectal temperature of 103° F., and slight pharyngeal injection. As he had not improved by the next morning, he was hospitalized with the diagnosis of questionable poliomyelitis. A lumbar puncture revealed 23 white blood cells per cubic millimeter of cerebrospinal fluid. As it was believed that the diagnosis of poliomyelitis was established, he was transferred to this hospital. There had been no known exposure to contagion.

Physical examination showed an alert, well-developed, well-nourished white male infant with a temperature of 103° F. by rectum and who did not appear acutely ill. There was slight injection of the pharynx and eardrums. The examination was otherwise normal.

Laboratory data revealed a normal red blood count. The white blood count was 6,900 cells per cubic millimeter, of which 52 per cent were polymorphonuclears and 47 per cent were lymphocytes. Many of the latter were large and atypical. Dick and Shick tests were positive. A heterophil antibody determination and a tuberculin test in 1/1,000 dilution were negative. A nose and throat culture grew pneumococci and *Staphylococcus aureus* in moderate numbers.

Course.—The patient was admitted with the differential diagnosis of roseola, abortive poliomyelitis, nasopharyngitis with mild bilateral otitis media, and infectious mononucleosis. On the second hospital day his temperature returned to normal and several suboccipital nodes appeared. His general condition remained good. On the following day he had a transient temperature spike of 101° F. by rectum. A repeat white blood count showed 6,600 cells per cubic millimeter with a differential count of 73 per cent lymphocytes, all of which had normal morphology. A lumbar puncture revealed clear fluid under normal pressure with a normal protein content, a sterile culture, 350 red blood cells, and 4 mononuclear cells per cubic millimeter. On the fourth hospital day, the seventh day of the disease, he developed a brownish-red macular rash on the face, chest, and abdomen which began to fade after twenty-four hours. At no time was there conjunctivitis, photophobia, Koplik spots, or cough. He was discharged home on the fifth hospital day with the diagnosis of roseola.

CASE 5.—C. G. was admitted Sept. 9, 1931, and discharged Sept. 12, 1931.

This was the first admission of a 6-month-old white male infant who was admitted because of fever of three days' duration. The family history and past history were irrelevant.

The present illness started three days prior to admission, at which time the patient developed irritability, fever, and vomiting. The latter subsided after twenty-four hours, but the irritability and fever persisted. On the day of admission the mother noted that the anterior fontanel was bulging and that a rash had appeared. Physical examination revealed a generalized papular rash over the body and an anterior fontanel which was full and tense, projecting above the surface of the skull. There were no neurological signs and the eye-grounds were normal. The examination was otherwise negative.

Laboratory data was as follows: On the day of admission the hemoglobin was 85 per cent; the white count was 5,800 per cubic millimeter with a differential count of polymorphonuclears 61 per cent, lymphocytes 5 per cent; the cerebrospinal fluid showed a pressure of 350 mm. water (no mention was made as to the degree of relaxation of the patient), a negative Pandy test, a normal sugar content, and a cell count of forty mononuclear cells per cubic millimeter. On the following day, re-examination of the cerebrospinal fluid showed that the pressure had decreased and that there were thirty-seven white cells. On the third hospital day the cerebrospinal pressure was "slightly elevated," the Pandy test was negative, and the cell count was 20 cells per cubic millimeter, of which 10 were polymorphonuclears and 10 were monocytes. At no time were cultures of the cerebrospinal fluid positive. Throat cultures grew no pathogenic organisms. Tuberculin skin test in 1/1,000 dilution was negative.

Course.—The rash disappeared on the second hospital day, and the anterior fontanel did not become tense after the initial lumbar puncture. Except for a temperature elevation to 102° F. on the third hospital day, the patient was asymptomatic and was discharged on the fourth hospital day. A follow-up examination one month later revealed no abnormalities.

The ages of the above patients ranged from 6 months to 16 months. Three were boys and two were girls. Signs and symptoms referable to the central nervous system antedated the eruption by as much as seven days. One patient had coma and athetosis. One showed retraction of the neck, and one had stiffness of the neck. Three patients had bulging of the anterior fontanel, which, with their associated findings and subsequent course, warrants the diagnosis of serous meningitis or meningismus. The cerebrospinal fluid was normal in one patient but was under increased pressure in three patients and showed an increase in cell count in two patients. The white blood count was low in four patients and was slightly elevated in one patient. All patients had an uncomplicated course, and none demonstrated residual signs. However, one patient developed petit mal seizures one and one-half years later. In view of the family history of epilepsy, no conclusion can be drawn as to the possibility of the seizures being a sequela of roseola. As far as can be determined, roseola, even with the complication of central nervous system involvement, is a benign disease.

PRE-ERUPTIVE VARICELLA ENCEPHALITIS

Prior to 1935 reviews of the literature did not emphasize pre-eruptive varicella encephalitis.[21, 23, 33] Underwood, in his classic paper, reported eleven cases of varicella encephalitis, and in his review of the 109 cases previously reported, discovered eleven pre-eruptive cases.[22] From the available information the possibility that some of the patients might have had febrile convulsions cannot be excluded. Faust added one case[40] in which the differential diagnosis included tuberculous meningitis, poliomyelitis, staphylococcic meningitis, chickenpox

meningitis, and meningococcal meningitis, which demonstrates the variety of diseases this condition can simulate before the rash appears. In his case a vesicular eruption appeared eight days after the onset of symptoms.

In the cases in the literature, the symptoms appeared from twelve hours to eighteen days before the rash developed, averaging 3.8 days. These clinical manifestations included convulsions, agitation, headache, delirium, coma, and cerebellar ataxia, as well as the picture of acute anterior poliomyelitis, and meningoencephalitis. The cerebrospinal fluid findings were available in only one case and showed increased pressure, 1,000 "multinucleated" white cells per cubic millimeter, and a positive Pandy test.[40] All of the pre-eruptive cases cited by Underwood were reported as "cured," while twelve of the posteruptive patients died and sixteen showed sequelae. No pathologic data are available on the nature of the lesions in the pre-eruptive cases.

In his discussion of the six groups of neurological complications mentioned by Underwood, Masten emphasizes the importance of pre-eruptive manifestations by stating that an additional group could be composed of cases in which neurological symptoms preceded the eruption by a few hours or a few days.[41]

There has been no case of clearly defined pre-eruptive varicella encephalitis at the Children's Medical Center. One patient was seen who developed seizures and an eruption on the same day.

CASE 1.—A. D. G. was admitted May 15, 1947, and discharged May 23.

This was the first admission of a 3-month-old white male infant whose chief complaint was "spells of three weeks' duration." The family history and past history were noncontributory. The patient was born at full term by a normal delivery, breathed spontaneously at birth, and had no neonatal distress.

The present illness began three weeks prior to admission when, after a known exposure to chicken pox, the patient developed varicella. On the same day that the first skin lesion appeared, the patient began to have episodes occurring three to four times daily and lasting five to six minutes in which he became unresponsive, stiffened his arms and legs, and arched his back. The exact time relationship of the appearance of the rash and the occurrence of seizures is not known.

Physical examination on admission showed a normal temperature, and the residual of a few chicken pox lesions on the legs. The patient appeared alert, vigorous, and without evidence of convulsions. The anterior fontanel was flat, and the neurological examination was normal.

Laboratory studies showed a normal urinalysis, hemoglobin, and white blood count. Lumbar puncture revealed clear spinal fluid with normal pressure, normal sugar, no cells, sterile culture, and a total protein of 69.4 mg. per cent. Subdural taps were dry bilaterally. The nonprotein nitrogen, serum calcium, phosphorus, and phosphatase were normal. An electroencephalogram showed a grossly slowed record with spikes in all leads. X-rays of the skull were normal.

Course.—During his hospital stay he had almost daily episodes which began with a sharp cry and consisted of a jerking and tightening of the muscles of the extremities occurring at thirty-second intervals ten to twelve times in succession and associated with vomiting. He was discharged with the diagnosis of acute encephalitis due to chicken pox.

The patient was re-admitted two months later for re-evaluation. An interval history showed that he had continued to have several seizures weekly of the type previously described. At the age of five and one-half months he could not

roll over, and could not sit without support. Physical examination revealed a well-developed, well-nourished infant who had a suggestion of a tonic neck pattern. The reflexes in the lower extremity were hyperactive, but there was no clonus. The remainder of the examination was negative. Cerebrospinal fluid was under normal pressure, was clear, and had a normal sugar content, normal cell count, and total protein of 53.1 mg. per cent. An electroencephalogram was reported as a slowed record with a few 2 and 3 per second waves, but no focus or seizure discharges. Following discharge the patient continued to have seizures and degenerated rapidly, dying of pneumonia one year later

DISCUSSION

Instances of clinical meningitis and encephalitis seen at this hospital complicating the pre-eruptive phase of rubeola, rubella, roseola, and varicella have been cited. The symptoms, signs and laboratory findings, course, and prognosis of our patients with rubeola encephalitis did not differ from those previously reported. The above case of pre-eruptive rubella encephalitis is the first to be reported as far as we could determine. This patient had a known exposure to rubella, developed encephalitic symptoms three and one-half days before the rash appeared, had normal cerebrospinal fluid, a leucocytosis, and had some residual ataxia and personality changes. That leucocytosis occurs in conjunction with the encephalitic complications of the above-named diseases which are usually associated with a leucopenia, is a well recognized fact.[2, 12, 36] The cases of roseola differed from those described in the literature in that athetosis occurred in one patient, elevated cerebrospinal fluid pressure in three patients, and an increased number of white blood cells in the cerebrospinal fluid of two patients. The case of varicella encephalitis cited cannot be strictly classified as belonging to the pre-eruptive group.

The diagnosis of pre-eruptive meningoencephalitis cannot definitely be established until the appearance of the eruption. However, it can be strongly suspected when one is considering a patient with the history of an acute onset of symptoms indicative of central nervous system involvement plus a history of recent exposure to measles, chicken pox, rubella, or roseola. Physical examination of such patients is typical only in that an encephalitic picture or signs of meningeal irritation are found and does not differ from that seen in the post-eruptive types. It may be impossible to differentiate this picture from that of febrile convulsions and postconvulsive state without a period of observation. The cerebrospinal fluid may be normal or may show nonspecific changes of increased pressure, increased protein, and/or increased number of cells, usually mononuclear. In contrast to the eruptive phase, the blood examination may show a leucocytosis. When confronted with a patient who has an acute process involving the central nervous system and a history of exposure to contagion, it is to be emphasized that, although the two are in all probability related, it would be unwise merely to await the appearance of the rash without carefully ruling out other possible etiological factors, particularly those disturbances which demand specific and immediate therapy.

The fact that the encephalitis can occur prior to the appearance of the rash in the common eruptive contagious diseases would seem to be well estab-

lished, although experienced observers in the field of infectious diseases have in the past expressed doubt.[45, 49] However, such a diagnosis is purely a clinical one and has not been confirmed by pathologic data.

SUMMARY

The literature concerning the appearance of neurological symptoms prior to the onset of the eruption in the common eruptive contagious diseases has been reviewed and the experience of this hospital during the past twenty years with the condition has been summarized. Pre-eruptive encephalitis or encephalomyelitis should be included in the differential diagnosis of any childhood disease which presents acute neurological symptoms of unknown etiology.

Grateful acknowledgment is given to Dr. R. Cannon Eley for his invaluable criticisms in the preparation of this paper.

REFERENCES

1. Ford, F. R.: Nervous Complications of Measles, Bul. Johns Hopkins Hosp. **43**: 140, 1928.
2. Hamilton, P. M., and Hanna, R. J.: Encephalitis Complicating Measles, Am. J. Dis. Child. **61**: 483, 1941.
3. Litvak, A. M.: Encephalitis and Encephalomyelitis Complicating Measles, Arch. Pediat. **64**: 507, 1947.
4. Hoyne, A. L., and Slotkowski, E. L.: Frequency of Encephalitis as a Complication of Measles, Am. J. Dis. Child. **73**: 554, 1947.
5. Nervous Complications of Measles, New Zealand Med. J. **35**: 101, 1936.
6. Applebaum, E., et al.: Measles Encephalitis, Am. J. Dis. Child. **77**: 25, 1949.
7. Malamud, N.: Encephalomyelitis Complicating Measles, Arch. Neurol. & Psychiat. **38**: 1025, 1937.
8. Moore, E., and McCordock, H. A.: Encephalomyelitis and "Hemorrhagic Virus Pneumonia" Complicating Measles, Arch. of Neurol. & Psychiat. **32**: 560, 1934.
9. Ferraro, A., and Scheffer, I. H.: Encephalitis and Encephalomyelitis in Measles, Arch. Neurol. & Psychiat. **25**: 748, 1931.
10. Parrish, J.: Nervous Symptoms Complicating Measles, Brit. J. Med. **1**: 1159, 1936.
11. Davidson, C., and Friedfeld, L.: Acute Encephalomyelitis Following German Measles, Am. J. Dis. Child. **55**: 496, 1938.
12. Margolos, F. J., et al.: Post Rubella Encephalomyelitis, J. PEDIAT. **23**: 158, 1943.
13. Read, C. F.: Meningo-encephalitis and Rubella, J. A. M. A. **109**: 654, 1937.
14. Brock, J. H. E.: Meningo-encephalitis Following Rubella, Lancet **2**: 1190, 1929.
15. Briggs, J. F.: Meningo-encephalitis Following Rubella, J. PEDIAT. **7**: 609, 1935.
16. Merritt, H. H., and Koskoff, Y. D.: Encephalopathy Following German Measles, Am. J. Med. Sci. **191**: 690, 1936.
17. Barraclough, W. W.: German Measles Encephalomyelitis, Canad. Med. Assoc. J. **36**: 511, 1937.
18. Humphrey, T. F., and Ekermeyer, E. W.: Rubella: Report of an Epidemic With an Unusual Number of Complications and Relapses, Ohio State Med. J. **33**: 406, 1937.
19. Baumgartner, E. A.: Encephalitis Following German Measles, N. Y. State J. Med. **36**: 907, 1936.
20. Schaffer, J. D.: Encephalomyelitis Complicating Measles, S. Africa Med. J. **15**: 32, 1941.
21. Yannett, H., et al.: Varicella Encephalitis, Arch. Neurol. & Psychiat. **26**: 322, 1931.
22. Underwood, E. A.: Neurological Complications of Varicella, Brit. J. Dis. Child. **32**: 83, 1935.
23. Brain, W. R.: Zoster, Varicella, and Encephalitis, Brit. Med. J. **1**: 81, 1931.
24. Fry, F. M.: Case of Encephalitis Following Varicella, Canad. M. A. J. **27**: 284, 1932.
25. Swyer, R.: Varicella With Encephalitis, Lancet **2**: 947, 1938.
26. Bridgeman, M. L.: Meningitis Complicating Mumps and Encephalitis Complicating Measles in the Same Child, Am. J. Dis. Child. **53**: 804, 1937.
27. Conrad, C.: Case of Encephalitis Secondary to Chicken Pox, Arch. Pediat. **46**: 716, 1929.
28. Taylor, R. J.: Meningo-encephalitis Following German Measles, M. J. Australian **2**: 604, 1937.
29. Rosenblum, J.: Roseola Infantum Complicated by Hemiplegia, Am. J. Dis. Child. **69**: 234, 1945.
30. Walefield, M. J.: Exanthem Subitum With an Encephalitic Onset, J. PEDIAT. **5**: 800, 1934.

31. Berenberg, W.: To be published.
32. Finley, K. H.: Pathogenesis of Encephalitis Occurring With Vaccination, Variola, and Measles, Arch. Neurol. & Psychiat. 39: 1047, 1938.
33. Eley, R. C.: Neurologic Conditions in Infants and Children, J. PEDIAT. 7: 248, 1935.
34. Bergman, R., and Magnusson, J. H.: Studie über Enzephalitis bei Varizellen mit besonderer Berüchsichtingung der Spätprognose, Acta Pediat. 26: 31, 1939.
35. Clemens, H. H.: Pre-Measles Encephalitis, J. PEDIAT. 22: 731, 1943.
36. Arena, J. M.: Pre-Measles Encephalitis, S. Med. J. 39: 513, 1946.
37. Goldbloom, A., and Keith, H. M.: Acute Encephalitis Following German Measles, Canad. M. A. J. 36: 181, 1937.
38. Wingo, S. M.: Encephalomyelitis Complicating Rubella, U. S. Navy Med. Bull. 45: 546, 1945.
39. Owen, A. B. S., et al.: Meningo-encephalitis Complicating German Measles, Med. J. Australia 2: 536, 1940.
40. Faust, O. A.: Chicken Pox Meningitis and Encephalitis, Arch. Pediat. 55: 29, 1938.
41. Masten, M. G.: Neurologic Complications of Chicken Pox, Arch. Pediat. 57: 749, 1940.
42. Price, H. W.: Measles Encephalitis, Canad. M. A. J. 36: 43, 1937.
43. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood, and Adolescence, ed. 2, Springfield, Charles C Thomas, Publisher, p. 601.
44. Christie, A., Hodes, H., and Weinstein, L.: Personal communication.
45. Jack, R. D. S.: A Rare Complication of German Measles, St. Barth.'s Hosp. J., War Bull. 1: 135, 1940.
46. Toomey, J. A.: in the discussion of Arena, J. M.: Pre-Measles Encephalitis, South. Med. J. 39: 513, 1946.
47. Stephens, E. W.: Ibid.
48. Ursule, James, and Freier, A.: Roseola Infantum, Arch. Dis. Child. 24: 54, 1949.
49. Brennemann, J.: Practice of Pediatrics, Baltimore, 1949, W. F. Prior Company, Inc., vol. 2, Ch. 11, page 17.

URINARY LYSOZYME

III. Lysozymuria in Children with the Nephrotic Syndrome

Armine T. Wilson, M.D., and William P. Hadley, M.D.
Wilmington, Del.

IN A previous paper[1] it was established that normal children excrete between 0 and 32 units of lysozyme per milliliter of urine. This range of values was found to include (with few exceptions) children with a wide variety of acute and chronic illnesses. However, some children with the nephrotic syndrome excreted lysozyme greatly in excess of the quantity encountered in normal children and in other disease states, reaching levels as high as 1,024 units per milliliter of urine.

It was hoped that by studying a group of nephrotic children for an extended period of time, the patterns of lysozyme excretions might be discovered, and the reason might become apparent why some children with the nephrotic syndrome excreted increased amounts of lysozyme, whereas others did not. The complex and chronic nature of the nephrotic syndrome, the difficulties which attend rational grouping of the patients on a clinical or biochemical basis, and the limited number of patients available for observation necessarily make difficult the drawing of conclusions concerning any apparent association between lysozyme excretion and other features of the disease. Unfortunately, we have had few patients available for study with acute hemorrhagic nephritis, chronic nephritis without nephrotic manifestations, and pyelonephritis, making it impossible to compare the findings in those diseases with the findings in the nephrotic syndrome.

Advantage has been taken of the high lysozyme excretion of some of the patients in the group to investigate the relationship of lysozyme output to time and to urinary volume. A study has also been made of the relationship of lysozymuria to proteinuria.

MATERIALS AND METHODS

Serial determinations were made of the urinary lysozyme of fourteen children in the clinically active stage of the nephrotic syndrome, of whom seven were females and seven were males. The clinical conditions of these patients were quite varied, but all had pitting edema, albuminuria, and hypoproteinemia. They had been ill for periods of four months to three years, eight months.

Urine was collected once a week from each patient for a period of approximately forty-eight hours. The urine specimens obtained from each patient were pooled and the total volume and the exact time interval covered by the collection period were noted. These specimens were kept in the refrigerator from the time of collection until determinations were made. No preservative was added. Most of the lysozyme determinations were made on these forty-eight-hour specimens. At approximately monthly intervals, urea clearance tests were performed on the patients, which made available carefully measured specimens over relatively

From the Alfred I. du Pont Institute of the Nemours Foundation.

short, successive periods of time. Lysozyme values were determined for some of these specimens.

In addition to the fourteen patients with the nephrotic syndrome in the clinically active stage, we have performed serial lysozyme determinations on the urine of four patients who were clinically quiescent.

A few urine specimens have been obtained from other hospitals from four other patients with the nephrotic syndrome and from one patient with pyelonephritis.

Urinary lysozyme was determined by the serial dilution method described elsewhere.[2] Urea clearance tests were performed by the method of Möller, McIntosh, and Van Slyke;[3] urinary protein by the method of Shevky and Stafford;[4] the concentration-sediment test by the method of Addis-Shevky,[5] in which the observed specific gravity was corrected for proteinuria; urea nitrogen by the method of Van Slyke and Kugel;[6] and plasma albumin and globulin by the methods of Van Slyke[7] and Kingsley.[8]

RESULTS

The largest amounts of urinary lysozyme encountered have been in children with the nephrotic syndrome. In Table I are summarized the urinary lysozyme findings of all the children studied, and it can be seen that the children with the nephrotic syndrome account for most of the hyperlysozymuric individuals. All children with the nephrotic syndrome did not, however, have hyperlysozymuria; and in certain individuals lysozyme excretion showed a change from elevated to normal or vice versa while under observation.

TABLE I. SUMMARY OF LYSOZYME EXCRETION OF ALL SUBJECTS*

CLASS OF PATIENT	NUMBER OF PATIENTS	LYSOZYME (UNITS PER ML. URINE)									
		0	4	8	16	32	64	128	256	512	1,024
Normal children	595	440	62	61	23	9	0	0	0	0	0
Nephrotic children	22	9	1	1	2	5	4	2	3	1	3
Miscellaneous diseases	144	106	15	12	6	3	1	0	1	0	0

*For the purposes of this tabulation, a patient is entered in the column which represents his *maximum* lysozyme excretion, although on performing serial tests, lower values may have been encountered in some of his other specimens.

1. Children With the Nephrotic Syndrome, Clinically Active.—Fourteen children in this class were followed serially over periods of two months to eight months. They were found to follow several patterns of lysozyme excretion. In Table II brief clinical and laboratory resumes are presented for five of the fourteen patients, exemplifying different patterns of lysozyme excretion.

(A) Four patients always excreted normal quantities of lysozyme. None of these patients had reduced urea clearance test values; one of the four showed a reduced ability to concentrate urine; none of them had nitrogen retention. The degree of hypoproteinemia was as severe in two of the four patients as in any individuals in the entire series. Proteinuria varied from slight to exceedingly high. From a clinical point of view, three of the four patients improved somewhat during the period of observation, one of them dramatically. The fourth patient underwent little change in clinical condition over a period of six months.

TABLE II. LYSOZYMURIA IN THE NEPHROTIC SYNDROME

A. LYSOZYME EXCRETION ALWAYS NORMAL

PATIENT	DATE (WEEK OF)	URINARY LYSOZYME (UNITS/ML.)	URINARY PROTEIN (GM./L.)	UREA CLEARANCE TEST (% NORMAL)	CONCENTRATION TEST	BLOOD UREA NITROGEN (MG./100 ML.)	PLASMA ALBUMIN, GLOBULIN (GM./100 ML.)	CLINICAL COMMENTS
1. C. W., girl aged 3 years	1/25/48	4	27.4	129.7		8.4	0.71, 3.66	
	2/ 1/48	8	6.5		1.026			
	2/ 8/48	4	18.0					
	2/15/48	8	7.6	250.8		6.6	0.88, 3.21	
	2/22/48	4	22.3					Fever, penicillin, sulfadiazine.
	3/ 1/48	8	25.2					
	3/ 7/48	8	14.4					
	3/14/48	0	36.0	186.1		7.4	0.68, 3.46	
	3/21/48	32	37.4					
	3/28/48	4	27.4		1.029	5.0	0.90, 3.58	
	4/ 4/48	4	13.0	238.7				Fever, penicillin, sulfadiazine.
	4/11/48	8	44.6					
	4/18/48	8	13.0		1.032	4.1	0.94, 3.23	
	4/25/48	8	51.8					
	5/ 2/48	8	54.7					
	5/ 9/48	16	10.1	311.8				
	5/16/48	8	2.2					
	5/23/48	8	<0.07		1.026			Edema has subsided.
	5/30/48	8	<0.07					
	6/ 6/48	8	<0.07	135.0		8.1	4.01, 2.49	
	7/ 1/48							Discharged, improved.

Onset, September, 1947. Edema, albuminuria, hypoproteinemia, elevated urea clearance, normal ability to concentrate urine, no hematuria, no hypertension, no nitrogen retention. Admitted to this hospital November, 1947. Course marked by several febrile bouts and occasional melena. Marked symptomatic and biochemical improvement in May, 1948. Discharged, improved. Diagnosis: nephrotic syndrome, cause undetermined. Probably nephrosis.

TABLE II.—CONT'D

B. LYSOZYME EXCRETION ALWAYS ELEVATED

PATIENT	DATE (WEEK OF)	URINARY LYSOZYME (UNITS/ML.)	URINARY PROTEIN (GM./L.)	UREA CLEARANCE TEST (% NORMAL)	CONCENTRATION TEST	BLOOD UREA NITROGEN (MG./100 ML.)	PLASMA ALBUMIN, GLOBULIN (GM./100 ML.)	CLINICAL COMMENTS
2. W. McN., a boy aged 3 years	1/25/48	512	18.0	23.6		37.3		
	2/ 1/48	512	23.8		1.013			
	2/ 8/48	256	20.2	23.9		41.5	1.01, 2.98	
	2/15/48	256	21.2					
	2/22/48	256	15.1					Fever, penicillin, and sulfadiazine.
	2/29/48	256	21.2	23.0		34.3	1.18, 2.94	Serum albumin, 175 Gm. I.V.
	3/ 7/48	256	38.9	27.3		37.6	1.47, 2.65	Serum albumin, 175 Gm. I.V.
	3/14/48	128	34.6					Serum albumin, 175 Gm. I.V. diuresis.
	3/21/48	256	37.4	25.0	1.012	25.7	3.31, 2.64	Edema reduced.
	3/28/48	1,024	24.5					
	4/ 4/48	512	20.2	26.1		36.6	1.28, 3.11	
	4/11/48	512	18.7					Fever, penicillin, sulfadiazine.
	4/18/48	128	15.8		1.012			
	4/25/48	256	27.4	27.0		30.2	1.26, 3.23	
	5/ 2/48	512	23.8					
	5/ 9/48	512	19.4					
	5/16/48		18.7					
	5/23/48	512	20.2		1.014			
	5/30/48	512	24.5					
	6/ 6/48	512	16.6	13.1		60.5		
	6/13/48				1.013			Coryza, sulfadiazine, edema.
	7/ 3/48	512	15.1					
	7/11/48	512	17.8	12.5		69.8	2.34, 2.68	Erysipeloid.
	7/18/48	512	18.0		1.012			
	7/25/48	1,024	23.8					
	8/ 1/48	1,024	24.1					Erysipeloid.
	8/ 7/48	512	25.2	6.6		95.8	1.61, 2.91	
	8/15/48	1,024	26.6					
	8/22/48	1,024	22.3	4.7		146.2	1.96, 2.35	
	8/29/48	512	23.7	1.2		167.7		
	9/ 5/48		25.2					Died.

Onset, April, 1947. Edema, proteinuria, hematuria, nitrogen retention, reduced urea clearance, reduced ability to concentrate urine, hyproteinemia, hypertension, and anemia. Admitted to this hospital September, 1947. Course in the hospital marked by clinical improvement followed by deterioration, progressing to anuria and uremia. Autopsy: chronic glomerulonephritis.

C. LYSOZYME EXCRETION FLUCTUATING

PATIENT	DATE (WEEK OF)	URINARY LYSOZYME (UNITS/ML.)	URINARY PROTEIN (GM./L.)	UREA CLEARANCE TEST (% NORMAL)	CONCENTRATION TEST	BLOOD UREA NITROGEN (MG./100 ML.)	PLASMA ALBUMIN, GLOBULIN (GM./100 ML.)	CLINICAL COMMENTS
3. E. L., girl aged 3 years	1/25/48	16	10.8					
	2/ 1/48	4	7.9		1.020			
	2/ 8/48	4	7.9	248.6		7.2	0.63, 2.94	
	2/15/48	16	12.2	149.4		6.0	0.39, 3.08	
	2/22/48	4	7.2					Fever, penicillin, sulfadiazine.
	2/29/48	0	10.1		1.019			
	3/ 7/48	4	13.7					
	3/14/48	32	10.1	159.7		5.5	0.52, 2.86	
	3/21/48	4	9.4					
	3/28/48	8	22.3					
	4/ 4/48	8	51.8	217.1		6.8	1.07, 2.46	Serum albumin, 175 Gm. I.V.
	4/11/48	4	10.1	264.6		5.2	0.97, 3.21	Erysipeloid.
	4/18/48	8	15.8		1.014			
	4/25/48	32	21.6					
	5/ 2/48	16	16.6					
	5/ 9/48	128	14.4	188.3		7.2	0.65, 2.90	
	5/16/48	128	14.0					
	5/23/48	16	11.5		1.017			
	5/30/48	16	17.3					
	6/ 6/48	16	15.8	106.8		10.4	0.96, 2.90	
	6/20/48				1.011			
	7/ 3/48	32	19.4					
	7/11/48	32	8.6	60.1		9.9	0.98, 2.82	
	7/18/48	32	17.6		1.015			
	7/25/48	64	15.5					Blood transfusion.
	8/ 1/48	64	26.6					
	8/ 7/48	64	18.0	64.8		12.5	1.11, 2.69	Erysipeloid.
	8/15/48	32	7.2					
	8/22/48	64	10.1					
	8/29/48	32	18.7	72.9	1.011	6.9	0.84, 2.97	
	9/ 5/48	16	11.9					Coryza, gross hematuria.
	9/12/48	16	14.4		1.010			
	9/19/48	16	14.4					
	9/26/48	32	13.0			13.0		Coryza, erysipeloid.
	10/ 3/48	64	20.9	71.4	1.012	12.0	0.80, 2.72	

Onset, March, 1947. Edema, albuminuria, hematuria, reduced urea clearance, reduced ability to concentrate urine, hypoproteinemia, no nitrogen retention, hypertension (?). Moderate anemia. Admitted to this hospital October, 1947. Course in the hospital has been irregular. Numerous febrile episodes. Diagnosis: nephrotic syndrome, probably due to chronic nephritis.

TABLE II.—CONT'D

D. LYSOZYME EXCRETION INCREASING

PATIENT	DATE (WEEK OF)	URINARY LYSOZYME (UNITS/ML.)	URINARY PROTEIN (GM./L.)	UREA CLEARANCE TEST (% NORMAL)	CONCENTRATION TEST	BLOOD UREA NITROGEN (MG./100 ML.)	PLASMA ALBUMIN, GLOBULIN (GM./100 ML.)	CLINICAL COMMENTS
	1/25/48			139.3		10.2	0.81, 3.22	Fever, coryza, penicillin, sulfadiazine.
4. L. E., girl aged 3 years	2/ 1/48	8	26.7					
	2/ 8/48	4	5.8	195.1		7.4	0.87, 3.69	Amigen, 50 Gm. I.V.
	2/15/48	16	27.4	96.9		14.2	0.53, 3.52	
	2/22/48	0	15.1					Fever, penicillin, sulfadiazine.
	2/29/48	4	20.2					
	3/ 7/48	8	25.2	85.4		13.0	0.59, 3.45	
	3/14/48	8	23.0					
	3/21/48	8	22.3					
	3/28/48	8	36.0	54.3	1.022	20.3	0.91, 2.85	Intermittent abdominal pain.
	4/ 4/48	32	36.0					
	4/11/48	128	28.8	29.0		33.0	0.88, 2.93	Abd. pain, peritoneal fluid sterile, hematuria.
	4/18/48	256	63.4	33.1		29.8	1.83, 2.55	Serum albumin 15 Gm. I.V. Hematuria.
	4/25/48	512	40.3		1.018			Hematuria.
	5/ 2/48	256	25.9	63.7		14.5	0.82, 3.21	Hematuria.
	5/16/48	128	23.0					Abdominal pain.
	5/23/48	256	29.5		1.016			
	6/ 6/48	256	28.4	24.6		45.5	0.82, 3.37	
	6/13/48				1.005			Xanthomata.
	7/ 3/48	512	28.7					
	7/11/48	256	27.4	35.7		22.0	1.05, 3.17	
	7/18/48	512	20.9		1.016			
	7/25/48	1,024	21.6					Abdominal pain, fever, penicillin, sulfadiazine.
	8/ 1/48	512	28.8	20.2		32.4	1.36, 3.09	
	8/15/48	1,024	19.3					Transfusion, whole blood.
	8/29/48	1,024	23.0		1.020			
	9/ 5/48	1,024	22.3	24.3		40.9	1.31, 3.10	
	9/12/48	512	21.6		1.012			
	9/19/48	1,024	24.5					
	9/26/48	1,024	25.2			47.1		Fever, penicillin, anuric.
	10/ 3/48	1,024	25.9	2.2		92.6	1.89, 3.20	Died.

Onset, August, 1947. Edema, albuminuria, hyproproteinemia, urea clearance, nitrogen retention, reduced ability to concentrate urine, hematuria, anemia. No hypertension. Admitted to this hospital January, 1947, course marked by numerous febrile episodes and gradual deterioration in condition. Terminal anuria and uremia. Autopsy: chronic glomerulonephritis.

deterioration in condition. Terminal anuria and uremia. Autopsy: chronic glomerulonephritis.

E. LYSOZYME EXCRETION DECREASING

PATIENT	DATE (WEEK OF)	URINARY LYSOZYME (UNITS/ML.)	URINARY PROTEIN (GM./L.)	UREA CLEARANCE TEST (% NORMAL)	CONCENTRATION TEST	BLOOD UREA NITROGEN (MG./100 ML.)	PLASMA ALBUMIN, GLOBULIN (GM./100 ML.)	CLINICAL COMMENTS
5. E. T., girl aged 10 years	1/25/48	256	7.9					
	2/ 1/48	256	7.9		1.017			
	2/ 8/48	256	10.1	44.5		18.7	1.08, 3.56	
	2/15/48	128	9.4					
	2/22/48	128	8.6	36.9		15.6	1.44, 3.21	Serum albumin, 175 Gm. I.V.
	2/29/48	256	19.4	30.8		12.6	2.63, 3.08	Discharged, improved.
	3/28/48	256			1.013	26.8	1.30, 3.28	Clinic visit. Doing well.
	6/17/48			47.0		19.9	1.64, 4.25	Clinic visit. Doing well.
	9/ 5/48	16		82.0		11.8	2.16, 2.90	Clinic visit. Doing well.
	1/ 3/49	8	3.9	91.4		11.0	3.56, 3.02	Clinic visit. Doing well.
	5/ 2/49	8	2.8	76.1		15.2	4.19, 3.14	Clinic visit. Doing well.

Onset, September, 1945. Edema, proteinuria, hypoproteinemia, reduced urea clearance, reduced ability to concentrate urine, moderate nitrogen retention, no hematuria, no hypertension. Admitted to this hospital June, 1946. Course marked by ups and downs in general clinical condition and several febrile episodes. Improved at time of discharge. Diagnosis: nephrotic syndrome, cause undetermined. Probably chronic nephritis.

(B) The lysozyme excretion of two patients was invariably elevated. Both were characterized by reduced urea clearance test values, reduced ability to concentrate urine, nitrogen retention, and profound disturbance of blood proteins. Both died and at autopsy the renal lesions were characteristic of chronic glomerulonephritis.

(C) Five patients showed considerable fluctuation in urinary lysozyme values, sometimes excreting normal and sometimes excreting elevated quantities, but not manifesting any well-marked trend toward persistently increased or persistently normal excretion. One of these patients died, and autopsy showed chronic nephritis and bilateral renal venous thrombosis. This patient's urinary lysozyme fluctuated between 32 and 64 units per milliliter of urine, values which are normal and slightly elevated. Her urea clearance test values were always low, her plasma proteins were reduced, and she had reduced ability to concentrate urine. Of the other four patients, all showed reduced ability to concentrate urine. The value of the urea clearance test in one of these children changed from elevated to reduced; in another it fluctuated from somewhat high to low, and in the other two it was usually reduced. Two patients showed moderate elevation of blood urea nitrogen at times, whereas the others always had normal blood urea nitrogen. The blood protein disturbances were profound in all four. Two of these patients showed slight clinical improvement toward the end of the period reported here, whereas the others were essentially unchanged in condition.

(D) Two patients showed a change in urinary lysozyme excretion from normal values to consistently elevated values. One of these patients died. During the period of increased lysozyme excretion both had reduced urea clearance test values, reduced ability to concentrate urine, nitrogen retention, reduced plasma albumin, and elevated plasma globulin. The patient who died developed terminal anuria and at autopsy the renal lesion was characteristic of chronic glomerulonephritis. The other patient improved clinically toward the end of the period of observation and was discharged from the hospital for care at home.

(E) One patient showed a change in urinary lysozyme excretion from elevated to normal values. This patient had reduced ability to concentrate urine, nitrogen retention, and hypoproteinemia when her lysozyme excretion was elevated. When it returned to normal values, there was a corresponding improvement in the value of her urea clearance test, in blood urea nitrogen, and in blood proteins.

2. Children With the Nephrotic Syndrome, Clinically Normal, With Proteinuria.—In addition to the fourteen patients described in the preceding paragraphs, we have performed serial urinary lysozyme determinations on a group of four patients whose only biochemical abnormality at the time of study was moderate proteinuria and who were asymptomatic clinically. None of these four patients excreted abnormal quantities of lysozyme in their urine.

3. Children With the Nephrotic Syndrome, Limited Observation.—Single urine specimens or a few specimens have been obtained from other hospitals

from four additional patients with the nephrotic syndrome and from one patient with a diagnosis of pyelonephritis. The patient with pyelonephritis excreted 64 units per milliliter of urine; two of the nephrotic children excreted 64 units per milliliter and the other two excreted 32 units per milliliter.

4. Time-Volume Studies of Urinary Lysozyme Excretion.—In order to determine whether or not the excretion of lysozyme in a patient with the nephrotic syndrome might be more constant per unit of time than per unit of urinary volume, an analysis was made of the lysozyme content of accurately timed urine specimens, the volume of which was carefully measured. The collections were subject to the error which inevitably accompanies the collection of urines in children.

TABLE III. TIME-VOLUME STUDIES OF URINARY LYSOZYME EXCRETIONS SUCCESSIVE SHORT-TIME INTERVALS*

PATIENT	TIME IN MINUTES	VOLUME (ML.)	LYSOZYME (UNITS/ML.)	LYSOZYME (UNITS/ PERIOD)	LYSOZYME (UNITS/ MINUTE)	URINE (ML./ MINUTE)
1. B. D.	157	53	32	1,696	10.8	0.34
	159	83	32	2,656	16.7	0.52
	152	49	32	1,568	10.3	0.32
	181	95	32	3,040	16.8	0.52
2. L. E. (1)	205	76	0	0	0	0.37
	350	158	8	1,264	3.6	0.45
	85	66	0	0	0	0.78
3. B. J. (1)	449	79	32	2,528	5.6	0.18
	88	107	4	428	4.8	1.22
	65	114	4	456	7.0	1.75
	60	101	4	404	6.7	1.68
4. W. McN.	643	232	512	118,784	184.7	0.36
	802	270	512	138,240	172.3	0.34
	618	140	512	71,680	115.7	0.23
5. D. W.	240	21	64	1,344	5.6	0.09
	225	67	128	8,576	38.1	0.30
	240	55	128	7,040	29.3	0.23
	70	50	128	6,400	91.4	0.71
	250	61	128	7,808	31.2	0.24
6. B. S.	262	24	64	1,536	5.9	0.09
	400	30	32	960	2.4	0.08
	135	16	64	1,024	7.6	0.12
	515	74	64	4,736	9.2	0.14
7. C. W.	300	30	4	120	0.4	0.10
	255	33	32	1,056	4.1	0.13
	480	58	4	232	0.5	0.12
8. S. F.	72	78	256	19,968	277.3	1.08
	20	10	256	2,560	128.0	0.50
	50	46	256	11,776	235.2	0.92
	60	70	256	17,920	298.7	1.17
9. L. E. (2)	315	50	128	6,400	20.3	0.16
	330	47	256	12,032	36.5	0.14
	595	144	128	18,432	30.9	0.24
10. B. J. (2)	229	56	128	7,168	31.3	0.25
	146	108	64	6,912	47.3	0.74
	170	100	64	6,400	37.6	0.59
	50	50	64	3,200	64.0	1.00

*Urine collected over accurately timed, short, successive intervals.

Table III shows the excretion of a group of ten children during successive, short-time intervals. In the fourth column it can be seen that in successive periods of time lysozyme excretion per unit of urinary volume was sometimes constant in quantity but more often varied considerably, in two instances as much as eight times in immediately successive periods. In the sixth column it is seen that the excretion of lysozyme per unit of time varied as much as sixteen times during immediately successive periods. In some of the tests [Table III, D. W. (5) and S. F. (8)], when the urinary flow per minute increased, the lysozyme output also increased and vice versa. This was not always the case, however [Table III, B. J. (1) and L. E. (2)]. There appears to be no advantage in expressing lysozyme excretion on a time rather than a volume basis.

In Table IV are shown the time-volume relationships over longer periods of time than those represented in the preceding paragraph. In this case, at weekly intervals, voidings over a period of approximately forty-eight hours were combined and pooled and the lysozyme content per milliliter of urine was determined. It can be seen that the excretion of lysozyme per millimeter of urine varied in individual patients from week to week as much as eight times, and that on a time basis, the excretion varied as much as 3.6 times.

TABLE IV. TIME-VOLUME STUDIES OF URINARY LYSOZYME EXCRETION: POOLED FORTY-EIGHT-HOUR SPECIMENS AT WEEKLY INTERVALS*

PATIENT	DATE	COLLECTION PERIOD IN HOURS	VOLUME OF URINE (ML.)	LYSOZYME (UNITS PER ML.)	LYSOZYME (UNITS PER PERIOD)	LYSOZYME (UNITS PER MIN.)
1. N. B.	1-25	39.5	1,300	8	10,400	4.39
	2-1	48.5	1,330	8	10,640	3.66
	2-8	48.0	1,180	4	4,720	1.64
	2-15	47.5	1,080	4	4,360	1.52
	2-22	48.0	1,460	8	11,680	4.06
2. B. D.	1-25	48.0	1,600	32	51,200	17.8
	2-1	49.0	960	32	30,720	10.5
	2-8	48.0	1,070	16	17,120	5.9
	2-15	39.0	910	16	14,560	6.2
	2-22	48.0	960	64	61,440	21.3
3. B. J.	1-25	48.0	770	32	24,640	8.6
	2-1	46.0	370	64	23,680	8.6
	2-8	47.0	1,330	8	10,640	3.8
	2-15	48.0	440	64	28,160	9.8
	2-22	49.5	760	16	12,160	4.1
4. E. L.	1-25	48.0	530	16	8,480	2.9
	2-1	34.5	930	4	3,720	1.8
	2-8	48.0	1,050	4	4,216	1.5
	2-15	48.0	980	16	15,680	5.4
	2-22	47.5	1,050	4	4,200	1.5
5. E. T.	1-25	46.0	4,380	256	1,121,280	439.4
	2-1	54.0	4,840	256	1,239,040	382.4
	2-8	46.0	3,100	256	793,600	287.5
	2-15	47.0	2,910	128	372,480	132.1
	2-22	42.0	3,320	128	424,960	168.6
6. B. S.	1-25	35.5	520	64	33,280	15.6
	2-1	48.0	540	64	34,560	12.0
	2-8	36.0	480	32	15,360	7.1
	2-15	40.0	560	64	35,840	14.9
	2-22	40.0	590	64	37,760	15.7

*Urine collected over approximately forty-eight-hour periods and pooled at weekly intervals.

It is thus apparent that the lysozyme output of a particular patient is not strictly uniform on either a time basis or a urinary volume basis, and that the variability of lysozyme content per unit of urinary volume in specimens collected over short, successive time periods is about the same as that in specimens collected and pooled over two-day periods at weekly intervals.

5. Relation of Proteinuria to Lysozymuria.—Since we first sought lysozyme in the urine of nephrotic children because of their proteinuria, we have investigated the question whether the excretion of abnormal quantities of the protein, lysozyme, was merely a reflection of the disordered physiological state in which other proteins appear in the urine to excess. We have encountered many urine specimens which have contained large quantities of protein without an associated elevation of lysozyme content, and conversely, but less frequently, we have found abnormal quantities of lysozyme to be present in urine specimens in which the total protein content was not elevated. An example of the first situation was a specimen of urine from a child with the nephrotic syndrome which contained 29.0 Gm. of protein per liter but only 4 units per milliliter of lysozyme, a normal value. An example of the second situation was a patient who excreted 64 units of lysozyme per milliliter in a urine of normal protein content (less than 0.07 Gm. per liter).

We were fortunate to obtain urine specimens from a patient in St. Christopher's Hospital, Philadelphia, with orthostatic albuminuria. A urine specimen obtained when the patient had been resting horizontally contained 0.22 Gm. of protein per liter of urine and 8 units of lysozyme per milliliter of urine. After moderate exercise in the erect position, the patient's urinary protein increased to 4.32 Gm. per liter, but the lysozyme content remained 8 units per millilter.

It is clear that there was no direct quantitative correlation between proteinuria and lysozymuria, although in general the excretion of abnormal quantities of lysozyme was associated with abnormal proteinuria.

DISCUSSION

It is apparent that the excretion of abnormal amounts of lysozyme is not directly related to the essential pathologic disorder which, whatever it may be, is responsible for the nephrotic symptom-complex, since some of the children with well-marked nephrotic manifestations failed to have hyperlysozymuria. It is also suggestive that the patient with pyelonephritis, who did not have nephrotic symptoms, nevertheless had elevated urinary lysozyme. It is regrettable that we have been unable to obtain urine specimens from patients with chronic nephritis but without nephrotic manifestations.

A good explanation cannot be offered for the difference in lysozyme excretion in the children who did and who did not excrete elevated quantities of lysozyme. At first glance it appeared that increased or borderline excretion of lysozyme was encountered in the patients who were considered to have chronic nephritis with impaired renal function and that normal lysozyme excretion was present in patients whose clinical diagnosis appeared to be nephrosis or who were clinically quiescent. Since certainty in the clinical differentiation of chronic

nephritis from nephrosis is difficult to achieve until the disease has run its course, no rigid attempt has been made to classify the patients on such a basis, and we are reluctant to suggest at this time that a relationship exists between lysozyme excretion and the nature of the underlying disease process.

If, therefore, our attempt to discover an association between the degree of lysozyme excretion and other abnormalities in the nephrotic children is limited to a comparison of urinary lysozyme levels and other objective laboratory tests, it can be seen that hyperlysozymuria is not directly related to the extent of proteinuria or hypoproteinemia, but that in general those patients who had reduced urea clearance test values, nitrogen retention, and reduced ability to concentrate urine also had fluctuating or persistently elevated excretion of urinary lysozyme; that those patients whose urea clearance tests gave normal or increased values, whose ability to concentrate urine was unimpaired, and who did not have nitrogen retention, excreted, in general, normal quantities of lysozyme in their urine.

Infants born prematurely usually have reduced urea clearance test values for many months, yet the ten premature infants whose urine we tested did not excrete increased amounts of lysozyme.[1] This indicates that the association of reduced urea clearance and hyperlysozymuria which was observed in the children with the nephrotic syndrome is not a general phenomenon.

That hyperlysozymuria is not invariably associated with fatal outcome in the nephrotic syndrome is demonstrated by one patient, who, before death, excreted no more than 64 units of lysozyme per milliliter of urine.

There is no reason to believe that variations in lysozyme play a part in susceptibility or resistance to the infections which commonly occur in children with the nephrotic syndrome. No significant variations were noted in these patients during the infectious episodes which occurred while under observation.

It cannot be said with certainty what the source of urinary lysozyme is, although it is likely that it derives from the blood. Elucidation of this point awaits the development of an adequate method for measuring urinary and plasma lysozyme on a comparable quantitative basis.

From an etiological point of view, lysozyme, by its presence in certain secretions of the body, such as tears, nasal mucus, saliva, and sebum, serves a useful purpose by causing lysis of certain bacteria, thus denying them the possibility of survival in the human host. Although most of the microorganisms acted upon by lysozyme are considered saprophytes, it is entirely possible that they might be pathogenic if they were able to resist the lytic agent. It is difficult to imagine a function for lysozyme in the tissues and fluids of the interior of the body, where it is present in considerable quantity. Its bacteriolytic effect is of little value in such situations, and no physiologic role has been assigned to it.

Meyer and associates[9, 10] have recently shown that lysozyme acts on the protective mucus of the alimentary tract, although the nature of the action has not been elucidated and attempts to isolate a substrate for lysozyme action from mucus have not yet been successful. Those authors have advanced evidence suggesting an etiologic role for lysozyme in peptic ulcer and chronic ulcerative colitis. There is no reason at present to suspect that lysozyme plays any role in the pathogenesis of the disorders of children with the nephrotic syndrome.

SUMMARY

1. In contrast to healthy children and children with miscellaneous diseases who rarely excreted more than 32 units of lysozyme per milliliter of urine, ten out of fourteen children with the nephrotic syndrome excreted increased quantities, from 64 to 1,024 units of lysozyme per milliliter of urine.

2. Several patterns of lysozyme excretion were observed among the children with the nephrotic syndrome. Their urinary lysozyme values were: (A) always normal, (B) always elevated, (C) fluctuating and borderline, (D) ascending, or (E) descending.

3. No clearcut correlation existed between the excretion of lysozyme and other manifestations of the nephrotic syndrome, although in general patients with reduced urea clearance test values, reduced ability to concentrate urine, and nitrogen retention excreted borderline or increased amounts of lysozyme, whereas patients with elevated urea clearance test values, normal ability to concentrate urine, and normal plasma urea nitrogen excreted normal amounts of lysozyme.

4. The degree of lysozymuria was not related to the severity of proteinuria or hypoproteinemia.

5. The quantity of lysozyme excreted per millimeter of urine often varied in a given patient during successive short periods of time and from week to week. The quantity of lysozyme excreted per minute also varied. In some instances the amount of lysozyme excreted by a particular patient increased as the urinary flow increased and vice versa, but this was not true of all patients at all times.

The authors are deeply indebted to Dr. L. E. Farr and Dr. J. F. Kramer for access to the children under their care with the nephrotic syndrome in the Alfred I. du Pont Institute, for urine specimens collected from them, and for permission to publish certain biochemical and clinical features of the patients for comparison with urinary lysozyme excretion.

REFERENCES

1. Wilson, A. T., and Hadley, W. P.: Urinary Lysozyme: II. Lysozymuria in Healthy Children and in Children With Miscellaneous Diseases, J. PEDIAT. 36: 45, 1950.
2. Wilson, A. T.: Urinary Lysozyme: I. Identification and Measurement, J. PEDIAT. 36: 39, 1950.
3. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. II. Methods, Baltimore, Md., 1932, Williams and Wilkins Co., p. 564.
4. Shevky, M. C., and Stafford, D. D.: A Clinical Method for the Estimation of Protein in Urine and Other Body Fluids, Arch. Int. Med. 32: 222, 1923.
5. Addis, T.: The Renal Lesion in Bright's Disease, Am. J. Med. Sc. 176: 617, 1928.
6. Van Slyke, D. D., and Kugel, V. H.: Improvements in Manometric Micro-Kjeldahl and Blood Urea Methods, J. Biol. Chem. 102: 489, 1933.
7. Peters, J. P., and Van Slyke, D. D.: Quantitative. Clinical Chemistry, vol. 2, Methods, Baltimore, 1932, Williams & Wilkins Co., pp. 355, 691.
8. Kingsley, G. R.: A Rapid Method for the Separation of Serum Albumin and Globulin, J. Biol. Chem. 133: 731, 1940.
9. Meyer, K., Prudden, J. F., Lehman, W. L., and Steinberg, A.: Lysozyme Activity in Ulcerative Alimentary Disease, I. Lysozyme in Peptic Ulcer, Am. J. Med. 5: 482, 1948.
10. Meyer, K., Gellhorn, A., Prudden, J. F., Lehman, W. L., and Steinberg, A.: Lysozyme Activity in Ulcerative Alimentary Disease, II. Lysozyme Activity in Chronic Ulcerative Colitis, Am. J. Med. 5: 496, 1948.

THE INCIDENCE OF CONGENITAL IMPATENCY OF THE NASOLACRIMAL DUCT

EDWIN L. KENDIG, JR., M.D., AND DUPONT GUERRY III, M.D.
RICHMOND, VA.

AS far as we can determine, there has been no satisfactory study of the incidence of congenital impatency of the nasolacrimal duct. Most pediatricians are aware of the common occurrence of this condition, but many cases are still thought to be "stubborn conjunctivitis." Except for our original study,[1] in which we reported an incidence of 6 per cent in a series of 200 unselected, consecutive, full-term infants, no attempts has been made to determine the true incidence of this condition. Since that relatively small study was published, we have extended the series to 1,000 newborn infants and have observed fifty-seven cases (5.7 per cent) of congenital impatency of the nasolacrimal duct (Table I). This seems to indicate that the incidence determined in the first study was statistically accurate.

TABLE I.

NEWBORN INFANTS	NO. AFFECTED	PERCENTAGE
200	12	6.0
800	45	5.6
1,000 (total)	57 (total)	5.7

The only other figures on the incidence of this condition which we have been able to find are those of Stephenson[2] and Kipp.[3] The former observed that 1.75 per cent of 1,538 children in the outpatient department of a children's hospital had a lacrimal obstruction since birth, and the latter stated that 10 per cent of all cases of dacryocystitis occur in children under one year of age. In neither survey was any effort made to include those cases which cleared spontaneously.

DISCUSSION

The cases studied in this series were unselected, consecutive, full-term newborn infants at the Medical College of Virginia, Hospital Division, St. Luke's Hospital, Retreat for the Sick, Stuart Circle Hospital, and Johnston-Willis Hospital.

The diagnostic criteria were the presence of epiphora and the appearance of mucopus after pressure over the affected lacrimal sac.

Treatment consisted of local application of a penicillin ointment containing 1,000 Oxford units per gram of ointment base three times daily, and massage by the mother over the region of the sac.

Since many of these patients were from outlying towns and districts, follow-up in this series was not satisfactory. However, in our original study, there was a satisfactory follow-up, and from that we concluded that the vast majority of such cases clear under the conservative treatment outlined above. We have arbitrarily set six months as the period during which conservative therapy should be tried. It is our feeling that few cases clear after that time without benefit of probing.

In those cases in which probing must be carried out, it should be done with the patient under general anesthesia and not as an office procedure. The procedure which we have found to be most satisfactory is the introduction of the Number 1 Bowman probe through the superior punctum and canaliculus after dilation of the punctum with the dilator, with the patient under ether anesthesia. The inferior meatus is explored with a submucous elevator and the probe located and rubbed until bare metal is felt.

Probing should not be delayed because of the presence of mucopus, since in these particular instances infection is eradicated only after patency has been established. The possibility of establishing a false passage and introducing pyogenic material into the surrounding tissue is remote and has not occurred in our experience, nor should it occur if probing is carried out as previously outlined.

In our opinion there is little factual basis for the old belief that the instillation of silver nitrate into the newborn infant's eye (Credé's procedure) can give rise to impatency of the nasolacrimal duct. The final answer to this question will come only when penicillin or other antibiotic prophylaxis against ophthalmia neonatorum supersedes Credé's silver nitrate method.

SUMMARY

In a study of 1,000 consecutive, unselected, full-term newborn infants, fifty-seven cases (5.7 per cent) of congenital impatency of the nasolacrimal duct were found.

REFERENCES

1. Guerry, D., and Kendig, E. L.: Congenital Impatency of the Nasolacrimal Duct, Arch. Ophthalmol. 39: 193, 1948.
2. Stephenson, S.: A Preliminary Communication on Affections of the Tear Passages in Newly Born Children, M. Press and Circ. 119: 103, 1899.
3. Kipp, C. J.: Dacryocystitis in Nursing Infants, T. Am. Ophth. Soc. 2: 537, 1879.

THROMBOSIS OF THE RENAL VEIN IN INFANTS

CHARLES Q. MCCLELLAND, M.D., AND JAMES P. HUGHES, M.D.
CLEVELAND, OHIO

THROMBOSIS of the renal vein in infants causes a rarely diagnosed syndrome characterized by sudden onset of hematuria or anuria, shock, and appearance of palpable lateral abdominal masses in an infant usually suffering from dehydration as a result of a severe diarrheal disorder.

Since Rayer's[1] initial description of thrombosis of the renal vein in infancy in 1837, cases have been described in the older European literature by Pollak,[2] Hutinel,[3] and Oppenheim,[4] and in the more recent European literature by Morison[5] and by Behr.[6] However, relatively few reports have appeared in the American literature. In 1942 Campbell and Matthews[7] described thrombosis of a renal vein in two infants. The first case was diagnosed at autopsy. In the second case the clinical diagnosis was proved at operation; this was the first reported case of thrombosis of the renal vein in infancy which had been accurately diagnosed clinically and verified at operation or autopsy.

In the eight-year period from 1941 to 1948 inclusive, renal vein thrombosis with infarct of the kidney was encountered in three cases of 328 consecutive autopsies performed on full-term infants who survived for at least twenty-four hours after delivery but died before the age of 12 months. Severe diarrhea was the predominant clinical finding in thirty-one cases, including the three under discussion. Thus renal vein thrombosis appears as a significant complication of diarrheal disease in infancy.

It is the aim of this paper to present these three cases of thrombosis of the renal vein with renal infarction, including the second and third reported cases in which the diagnosis was made and verified, to discuss the clinical and pathological features, and to emphasize the urgency of instituting therapy.

CASE 1.—Baby boy S. was admitted Sept. 2, 1941. This 8-day-old white male infant was born in a neighboring hospital following a difficult forceps delivery resulting in lacerations of the scalp, face, and left ear. The labor was of seventeen hours' duration. The birth weight was 4.0 kg. The neonatal course was uneventful for the first four days, but subsequently the infant developed a persistent watery green diarrhea associated with vomiting of all feedings for three days prior to admission to Babies and Childrens Hospital. During this interval the infant lost 0.8 kg. in weight.

On admission the infant appeared to be poorly developed, poorly nourished, dehydrated with Kussmaul type of respiration, and acutely ill. The weight was 3.3 kg. The skin was of poor turgor with deep infected lacerations over the right parietal region of the scalp, over the left cheek, and behind the left ear. There were numerous small pustules over the arms, legs, and back and severe excoriations of the buttocks. A mucopurulent nasal discharge was present. The deep tendon reflexes were hyperactive and there was spasticity of the muscles of the extremities.

From the Department of Pediatrics and the Department of Pathology of Western Reserve University School of Medicine, and Babies and Childrens Hospital, Cleveland, Ohio.

Hemogram on admission showed 4.82 million erythrocytes per cubic millimeter, 97 per cent hemoglobin, leucocyte count of 8,900 per cubic millimeter with a differential count of 71 per cent neutrophils, 27 per cent lymphocytes, and 2 per cent monocytes. Urine on admission was of neutral reaction, gave a negative test for sugar and acetone, but gave a strongly positive test for albumin. Two to four leucocytes, thirty erythrocytes, and many granular casts per high-power field were found microscopically. Repeated urinalyses throughout the hospital course showed no change except for an increase in leucocytes to sixty cells per high-power field. The blood serological test for syphilis was negative. On the second hospital day the blood pH was 7.15, blood carbon-dioxide combining power 16.6 volumes per cent, nonprotein nitrogen 115, and creatinine 4.3 mg. per 100 c.c. On the third hospital day the blood pH was 7.35 and the carbon dioxide 25 volumes per cent.

On admission the patient was started on continuous intravenous fluids consisting of lactate Ringer's solution and 5 per cent glucose in saline. Despite nothing by mouth for twelve hours followed by small amounts of water every two hours, the infant continued to have a watery diarrhea which persisted throughout the entire hospital course. On the second hospital day the patient was continued on lactate Ringer's solution intravenously and subcutaneously and received a transfusion of 70 c.c. whole blood. At this time oral sulfathiazole, intramuscular vitamin K, and gavage feedings of casein milk were begun. By the fourth hospital day the patient was well hydrated, but had developed severe abdominal distention with associated cyanosis. Despite continued parenteral fluids, sulfathiazole, and oxygen, the patient's condition progressively deteriorated and he died on the fifth hospital day.

The clinical diagnoses in this case were acute gastroenteritis with secondary dehydration and acidosis, infected lacerations of the scalp, and bronchopneumonia.

Autopsy

The renal vein at the hilus of each kidney was occluded by a heterogenous red and gray friable thrombus.

The right kidney weighed 25.5 grams as compared with an expected weight of 15 grams. The capsule was thin and transparent and was stripped with ease from the smooth surface. The kidney was dark, purplish-red, and mottled with irregular, confluent, sharply demarcated foci of pale gray. On bisection against decreased resistance the cut surface was similarly mottled. The dark areas were firm while the pale areas were soft and friable. Distinction between cortex and medulla was not uniformly sharp. Firm, friable thrombi extended into interlobar and arcuate veins from the hilar portion of the renal vein.

The left kidney weighed 18 grams. A thin capsule was stripped with ease from a smooth, pinkish-brown surface which was discolored dark purplish-red at the lower pole. On bisection against normal resistance there was normally sharp distinction between cortex and medulla. The medulla at the lower pole was more deeply red than the overlying cortex. Thrombi extended into tributaries of the renal vein.

There was thrombosis of the superior sagittal and the right lateral venous sinuses of the dura mater. There was recent hemorrhage into the falx cerebri and recent subarachnoid hemorrhage involving both occipital lobes of the cerebrum. There was a soft, pale gray infarct of the spleen. The splenic vein contained no thrombus. There were recent deep lacerations of the right parietal region of the scalp, the right side of the face, and the posterior attachment of the left ear.

Microscopic Examination.—The right kidney had large foci in which there was loss of renal pattern except for occasional rings of pyknotic nuclei surrounded by masses of pale, acidophilic, finely granular material. There was widespread recent hemorrhage in the cortex. Occasional scattered glomeruli just beneath the surface had a normal pattern but were hyperemic. All other glomeruli were necrotic. Several large veins in the medulla contained mural thrombi composed of masses of amorphous acidophilic material, erythrocytes, and leucocytes. There were occasional polymorphonuclear leucocytes in the walls of these veins.

In the left kidney there was recent hemorrhage in the renal pyramids extending into the cortex along the medullary rays. There was disruption of some tubules in the hemorrhagic areas. Elsewhere, glomeruli and tubules were normal. Large veins in the cortex contained thrombi.

In the spleen there were large irregular foci of necrosis and hemorrhage. No thrombi were seen.

In the sagittal sinus there was a large thrombus of fibrin, erythrocytes, and leucocytes. There were a few lymphocytes and polymorphonuclear leucocytes in the vessel wall.

In a section of the right lung, a small artery in the middle lobe contained an irregular mass of acidophilic amorphous material partially covered by a layer of endothelial cells. The lumen of the vessel was narrowed and eccentric at this site.

Summary.—The patient had thrombosis of both renal veins, widespread infarction of the right kidney, recent hemorrhage of the left kidney, thrombosis of the sagittal and right lateral venous sinuses, recanalized thrombus or embolus in a small branch of the right pulmonary artery, recent infarct of the spleen; healing lacerations of the scalp and face.

CASE 2.—Baby girl M. was admitted Nov. 26, 1946. This 11-day-old white female infant was born in a near-by city following a normal term pregnancy and labor of three hours' duration. The delivery was uneventful and the birth weight was 2.4 kg. Except for slight icterus, which was noted on the second day but which had largely disappeared by the seventh day, the hospital course was uneventful and the patient was discharged on the seventh day weighing 2.2 kg. On the day following discharge from the hospital the patient had six yellow, semiliquid stools, and in the following three days she continued to have six to ten yellow, liquid stools daily. In the fourteen hours prior to her admission to Babies and Childrens Hospital she took only 4 oz. of formula. On the evening before admission her respirations became rapid and deep.

On admission the infant appeared normally developed, poorly nourished, dehydrated, and acutely ill. Respirations were deep, rapid, and grunting. Temperature was 38.2° C., pulse 160, respiratory rate 60, and the weight 2.0 kg. The skin was dry with poor turgor and diminished subcutaneous tissue. The anterior fontanel was depressed. There was moderate inflammation of the perineum and slight cyanosis of the fingers.

The erythrocyte count was 5.21 million per cubic millimeter, hemoglobin 110 per cent, leucocyte count 14,250 per cubic millimeter, with a differential of 8 per cent unsegmented polymorphonuclear cells, 10 per cent segmented neutrophils, 13 per cent myelocytes, 45 per cent lymphocytes, 3 per cent monocytes, and 21 per cent juvenile forms. On the day following admission the leucocyte count increased to 28,300 per cubic millimeter, the erythrocyte count fell to 2.8 million per cubic millimeter with a differential of 21 per cent unsegmented neutrophils, 26 per cent segmented neutrophils, 22 per cent lymphocytes, 4 per cent monocytes, 7 per cent juveniles, 16 per cent myelocytes, and 4 unidentified cells. Urine on admission was of a clear yellow color, acid reaction, and gave a strongly positive test for albumin. There were 25 to 30 leucocytes per high-power field and 2 to 3 granular casts. By the second hospital day the urine gave a 4 plus benzidine test for blood. Blood carbon-dioxide combining power on admission was 17.5 volumes per cent and the pH was 7.3. The following day the carbon dioxide was 53 volumes per cent and the pH was 7.35. Blood and stool cultures on admission and on the second hospital day were negative. *Escherichia coli* was cultured from blood collected immediately before death.

On admission the patient was given 10 per cent glucose in saline followed by 4 per cent sodium bicarbonate solution intravenously, lactate Ringer's solution subcutaneously, and penicillin intramuscularly. Within twelve hours after admission the patient was improved, alert, and afebrile. However, she had had twelve liquid stools during this period and had vomited all oral feedings. Because of the persistent vomiting all oral nourishment was discontinued and she was maintained on parenteral fluids. On the morning of the second hospital day the patient passed three stools flecked with bright red blood. Four hours later, while receiving a plasma transfusion, she became cyanotic, dyspneic, and developed abdominal distention. Administration of oxygen, caffeine, and epinephrine relieved the dyspnea and

cyanosis. Immediately thereafter a smooth 4 by 10 cm. mass was palpable in the left flank. X-rays of the abdomen and barium enema at this time showed no evidence of intestinal obstruction. Immediately thereafter the patient had two more blood-streaked stools, and developed gross hematuria. At this time a whole blood transfusion of 40 c.c. was given, and the patient was given 4.8 mg. of vitamin K intramuscularly. By the third hospital day the patient's condition was worse, with persistence of gross hematuria, a palpable flank mass, and râles throughout both lung fields. The patient's condition subsequently deteriorated rapidly and she died on the morning of the fourth hospital day.

The clinical diagnoses in this case were diarrhea of the newborn infant, infarction of the left kidney, bronchopneumonia, and sepsis.

Autopsy

The left renal vein was occluded by a mass of friable, reddish-brown material mottled with yellowish-gray. The left kidney weighed 41 grams as compared with an expected weight of 15 grams. The capsule was dark brown and thickened and was stripped with slightly increased resistance from a smooth, dry, dark red surface. On bisection against decreased resistance the cut surface was dark red and the medulla was irregularly mottled with foci of pale yellow. The line of demarcation between cortex and medulla was indistinct and cortical striations were not visible. The renal pelvis was normal. The left ureter was slightly dilated throughout its length and had a smooth gray mucosal surface.

The right kidney weighed 20 grams and was grossly normal.

The abdomen contained 50 c.c. of serosanguineous fluid. There was extensive recent left perirenal hemorrhage and recent hemorrhage into the left crus of the diaphragm. There were bilateral hemorrhagic bronchopneumonia and thrombosis of small vessels of the upper and middle lobes of the right lung.

Microscopic Examination.—In sections of the left kidney there were pale staining areas in the medulla with scattered small accumulations of hemosiderin scattered throughout necrotic tissue in which there was loss of cytological detail except for faint tubular outlines. These pale staining areas were surrounded by zones of recent hemorrhage extending into the cortex. In the hemorrhagic zones there were remnants of tubules and glomeruli. In the outer cortex there were foci of intact hyperemic glomeruli with a few adjacent normal tubules. Large veins in the medulla contained thrombi similar to those in the kidneys of Case 1. The lumen of the left renal vein was occluded by a thrombus composed of acidophilic amorphous material, erythrocytes, and leucocytes.

In sections of the right kidney there was hyperemia of the cortex and medulla. The lumens of numerous distal convoluted tubules were distended by brown-staining, coarsely granular material in which there were occasional lymphocytes. The epithelium of these tubules was the seat of cloudy swelling and at some sites was compressed into a thin layer of lining cells. Occasional limbs of Henle's loops contained well-preserved erythrocytes. In many glomeruli the subcapsular space was irregularly distended and contained pale acidophilic granular material. The veins and arteries were normal.

In sections of the lungs there was marked hemorrhagic bronchopneumonia. One medium-sized artery in the right lower lobe contained an adherent thrombus composed of a mass of pink fibrin strands and a few small and large mononuclear cells.

Sections of the thymus disclosed widespread recent hemorrhage into the interlobar connective tissue.

Summary.—The patient had thrombosis of the left renal vein, infarction of the left kidney, lower nephron nephrosis of the right kidney, recent left perirenal hemorrhage, hemoperitoneum, hemorrhagic bronchopneumonia bilateral, thrombosis of a medium-sized branch of right pulmonary artery, and recent interstitial hemorrhage of thymus.

CASE 3.—Baby boy R. was admitted Sept. 29, 1948. This 12-day-old white male infant was born in a near-by hospital following an uneventful pregnancy and normal labor of five hours' duration. The delivery was spontaneous with a cephalic presentation. The birth

weight was 3.3 kg. The neonatal course was uneventful until the sixth day, when the infant developed a watery yellow-green diarrhea shortly after discharge from the hospital. There was no blood, pus, or mucus in the stools; the diarrhea persisted until the ninth day with an average of fifteen stools daily. On the ninth day the formula was modified and subsequently the diarrhea became less severe. However, in the three days immediately prior to admission, the infant took only three feedings and developed marked listlessness.

Admission physical examination revealed an extremely dehydrated infant with ashen pallor. The weight was 2.8 kg. Temperature was 36.5° C., pulse 130, and respiration 65. The anterior fontanel was moderately full, the eyes were sunken, and the skin turgor was very poor, resembling that of sclerema. There was a slight serous discharge from the umbilicus and slight bleeding from the circumcision scar.

Hemogram on admission showed an erythrocyte count of 3.22 million per cubic millimeter, hemoglobin 71 per cent and leucocyte count of 35,000 per cubic millimeter, with a differential of 20 per cent segmented neutrophils, 30 per cent unsegmented neutrophils, 44 per cent lymphocytes, 3 per cent eosinophils, and 3 per cent monocytes. Urinalysis was never possible because of complete anuria. Lavage of the urinary bladder produced red fluid which gave a 4 plus benzidine reaction. On admission the blood carbon-dioxide combining power was 20.9 volumes per cent, the pH was 7.4, nonprotein nitrogen 123 mg. per 100 c.c., calcium 8.4, and phosphorus 11.7. On the second day the carbon dioxide was 30.3 volumes per cent, the pH 7.35, nonprotein nitrogen 123 mg. per 100 c.c., and potassium 5.3 meq. per liter. On the following day, the blood carbon dioxide was 43.1 volumes per cent, pH 7.3, and nonprotein nitrogen 143 mg. per 100 c.c. The cerebrospinal fluid was normal and was sterile on culture. Beta-hemolytic *Staphylococcus aureus* was cultured from the blood and from the umbilical stump. Stool cultures were sterile. No abnormalities of the chest or abdomen were seen on x-ray.

On admission, continuous intravenous fluids were begun. These consisted of 10 per cent glucose in water followed by glucose and Ringer's solution, lactate Ringer's solution, and Butler's solution. Intramuscular penicillin, streptomycin, and vitamin K were given. The patient was placed in an oxygen tent and started on lactic acid milk feedings. On the second hospital day parenteral fluids and chemotherapy were continued. The patient had a generalized convulsion which ceased after administration of calcium gluconate by vein. At this time firm masses were palpable in both flanks. Several hours later the respirations became Cheyne-Stokes in type and the infant developed generalized edema. There was twitching of the right hand. The condition became progressively worse and he died on the morning of the third hospital day.

The clinical diagnoses in this case were acute enteritis with severe diarrhea, severe dehydration, compensated metabolic acidosis, and renal vein thrombosis with secondary anuria.

Autopsy

The renal veins opened into the inferior vena cava in the usual manner. The right adrenal vein entered the vena cava directly; the left entered the left renal vein (Fig. 1). The right renal vein contained a firm, mottled red and gray thrombus which extended from the hilus of the kidney into the vena cava. In the vena cava the thrombus was elongated, reducing the size of the lumen, and was adherent to the wall as far cephalad as the orifice of the right adrenal vein. A thrombus filled the left renal and adrenal veins but did not extend into the vena cava. The renal arteries were normal.

The right kidney weighed 24 grams as compared with an expected weight of 15 grams. The capsule was thin, tense, and dark red. On bisection against decreased resistance there was a soft, dry, bulging, dark reddish-brown cut surface (Fig. 2). This discoloration was uniform throughout the parenchyma, obliterating the renal pattern.

The left kidney weighed 29 grams and was similar to the right except for irregular mottling with pale gray, most marked at the lower pole. The capsule was irregularly thickened by an accumulation of dark red friable clotted blood.

The ureters were patent and had small scattered accumulations of dark red, finely granular material adherent to the mucosa. The urinary bladder contained 5 c.c. of bright red fluid.

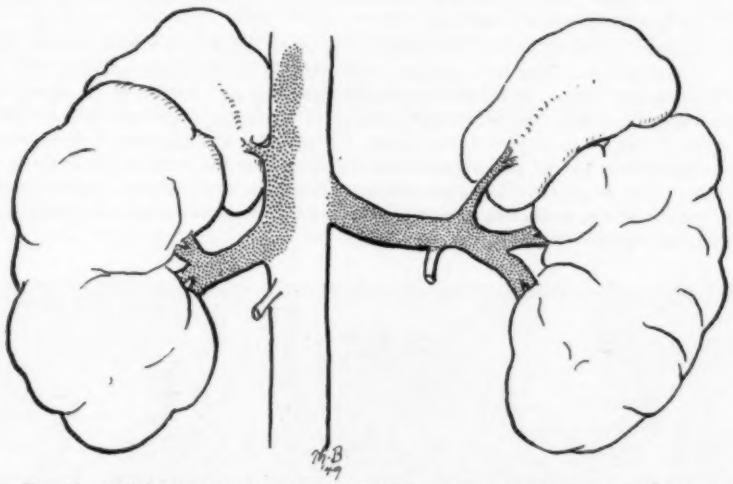


Fig. 1.—Case 3. Distribution of thrombus in the vena cava and the renal and adrenal veins.

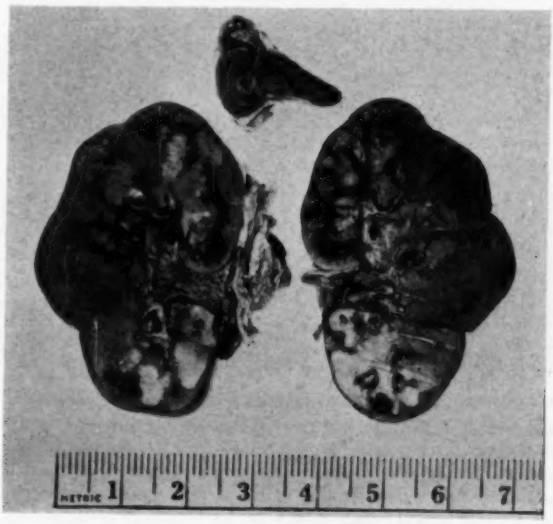


Fig. 2.—Case 3. Infarction of kidneys and of right adrenal.

The right and left adrenals each weighed 5.5 grams as compared with an expected total weight of 6.22 grams. The external surface of each was uniformly dark red and firm. The cut surface was dark red, smooth, and dry. In the central portion of each the adrenal vein was occluded by a firm, dark red, mottled thrombus.

The mucosal surface of the ileum had scattered irregular bright red foci of ulceration measuring up to 2 cm. in longitudinal dimension and 1 cm. in transverse. There was a similar ulcer measuring 1 cm. by 1 cm. in the cecum adjacent to the ileocecal valve.

There were firm mottled thrombi or emboli in the small branches of the pulmonary artery in the lower lobe of the right lung.

Microscopic Examination.—In sections of the right kidney there was uniform loss of pattern throughout the cortex and medulla. The remains of glomeruli consisted of rounded masses of pyknotic nuclei. Numerous larger, paler-staining scattered nuclei in various stages of degeneration were arranged in tubular pattern. A uniformly dense mass of pale shadowy erythrocytes formed a background throughout the sections, and through it were scattered numerous hematoidin burrs. Occasional isolated glomeruli at the outer surface of the cortex were intact. The large veins contained thrombi similar to those in the kidneys of Case 1. Smaller veins contained thrombi composed of erythrocytes with occasional fibrin strands. The pelvic mucosa was normal.

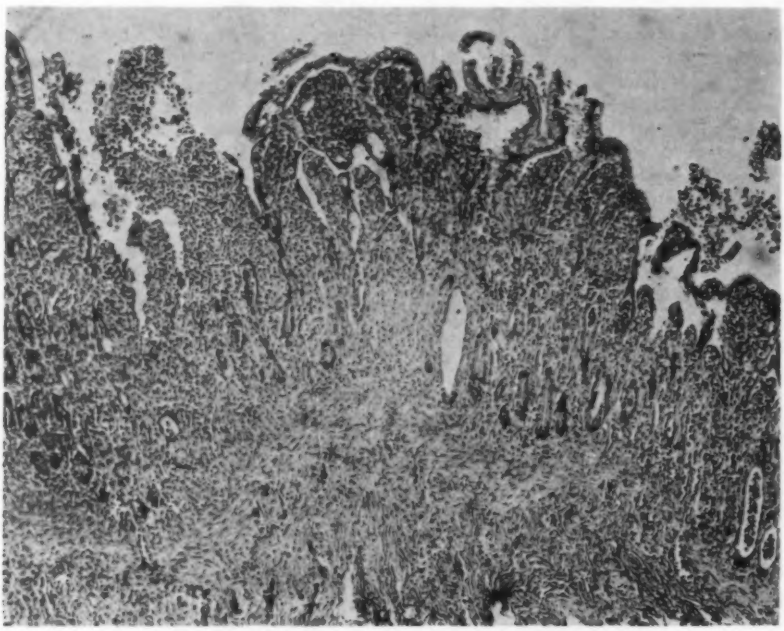


Fig. 3.—Case 3. Acute inflammation and ulceration of mucosa of ileum.

Sections of the right renal vein were occluded by an adherent thrombus composed of masses of acidophilic, amorphous hyalin material, erythrocytes, and leucocytes. At some sites there was early fibroblastic proliferation at the periphery of the thrombus.

Sections of the left kidney were similar except for foci of recent hemorrhage in the outer portion of the medulla. Intact hyperemic glomeruli in the outer cortex were more numerous than in the right kidney, and at some sites were surrounded by a few preserved tubules.

Both adrenals were necrotic except for a narrow peripheral zone in which there was fatty degeneration of cortical cells and infiltration of large and small mononuclear cells and polymorphonuclear leucocytes. The central vein of each adrenal contained a mixed thrombus. The arteries were normal.

Sections of the lungs disclosed two medium-sized arteries in the right lower lobe to contain masses of fibrin strands, pale-staining erythrocytes, and leucocytes. Two small arteries in the left lower lobe contained similar masses occluding the lumen of each. The vessel walls were normal. The lung parenchyma was normal.

In sections of the spleen there was a normal pattern. The splenic vein was filled with well-preserved erythrocytes, accumulations of hemosiderin, and small masses of hyalin material attached to the vessel wall at some sites.

Sections of the ileum disclosed foci of superficial ulceration of the mucosa with infiltration of large numbers of polymorphonuclear leucocytes and occasional eosinophils, plasma cells, and lymphocytes (Fig. 3).

On section of the umbilicus there was fibrous thickening of the vessel walls and extensive fibroblastic proliferation of the intima with marked narrowing of the lumen. There were polymorphonuclear leucocytes and occasional eosinophils scattered throughout the section. At one site there was a focus of necrosis surrounded by a few polymorphonuclear leucocytes.

Bacteriological Examination.—Heart's blood revealed no growth; urinary tract showed alpha hemolytic *Staphylococcus albus.*

Summary.—The patient had thrombosis of both renal and both adrenal veins, widespread infarction of the kidneys and adrenals, thrombi or emboli in small branches of the pulmonary artery bilaterally, thrombosis of the splenic vein, focal acute ulcerative ileocolitis, and acute omphalitis with abscess.

DISCUSSION

The important predisposing factor of renal vein thrombosis in the newborn infant is severe diarrhea, sometimes associated with definite ileocolitis as in Case 3. In a series of twenty-five autopsies on infants dying in an epidemic of diarrhea of the newborn infant, Barenberg and associates[9] found renal infarcts in five cases, and in two of these demonstrated thrombosis of a main renal vein.

Several factors tend to render the veins of the kidneys susceptible to thrombosis in infants. The precariousness of the water balance in the neonatal period is well known. The initial physiological weight loss, amounting to from 6 to 10 per cent of total body weight, is largely dehydrational, the result of a net loss of body water. This loss occurs chiefly through the lungs and skin, reaching a maximum deviation by the fourth day of life, after which blood hydration gradually begins to increase.[10] The onset of diarrhea during this early critical period, leading to further diminution in water content of the blood and increasing its viscosity, may favor intravascular clotting.

The nature of the renal circulation, with its double capillary network, results in considerable slowing of the stream in the renal veins and probably accounts for their predominance as a site of thrombosis. The relative frequency of this occurrence in infants may be associated with the uniformly low arterial and capillary pressures[11, 12] and presumably low venous pressure in the neonatal period.

There has been considerable discussion as to whether thrombosis of renal vessels in these cases arises in the main renal vein, in intrarenal radicles of the vein, or in capillaries. Hutinel[3] observed cases in which there was thrombosis of the main renal vein and its large intrarenal tributaries on one side, with thrombosis of only the latter in the other kidney. Morison[5] reported that the cellular reaction about the thrombi in the interlobar and arcuate veins suggested

that these were the primary foci of involvement in his cases. This was true also of our cases. Moreover, in the smaller veins of cortex and medulla of Case 3, there were thrombi composed of well-preserved erythrocytes and fibrin strands, considered of more recent origin than thrombi in the large veins of the same kidney (Fig. 4). In none of these kidneys was there thrombosis of capillaries, arterioles, or arteries. We therefore agree that the large intrarenal veins are most likely the vessels initially involved by thrombosis.

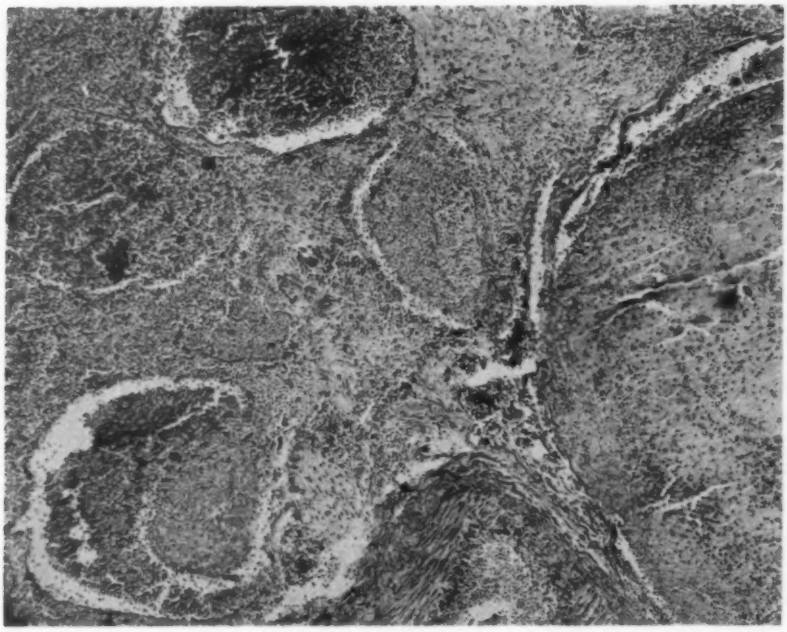


Fig. 4.—Case 3. Thrombi in one large and four small tributaries of the right renal vein.

An observation of interest in Case 2 was lower nephron nephrosis in the kidney not involved by thrombosis. Mallory[13] observed two constant factors in cases of lower nephrosis in battle casualties. In each there had been recovery from shock and pigment excretion. He reviewed the methods of the experimental production of the renal lesion and the theories of etiology, concluding that there is early onset of ischemia of the renal cortex in both traumatic and nontraumatic shock. This ischemia with reduced blood flow through the glomerular tuft, whether on a neurovascular basis or due to low systemic blood pressure, leads to anoxia of the distal segments of tubules. There follows a temporary functional disturbance manifested by oliguria and the rapid accumulation in the blood of nonprotein nitrogenous products. Anoxia probably explains the appearance of the first demonstrable morphologic change in the kidney, that is, lipoid vacuolization of the cells of the ascending limbs of Henle's loops. Next in the sequence of the development of the typical histologic feat-

ures is the precipitation of pigment in the lumens of the distal convoluted and collecting tubules. Whether or not the renal ischemia is sufficiently persistent to account for the later development of necrosis of these tubules is still unknown, but the presence of the pigment casts may be considered histologic evidence of at least temporary resumption of glomerular function.

In this infant there was clinical evidence of shock when the left flank mass appeared. In retrospect, the mass may be related to the development of venous thrombosis and infarction of the left kidney with hemorrhage. Immediately thereafter, a transfusion of whole blood had been given. This factor cannot be ruled out as the cause of the hemoglobinuric nephrosis. There were no clinical signs of transfusion reaction. However, death occurred forty-eight hours later. The histologic features of the right kidney were consistent with an early stage in the sequence of development of lower nephron nephrosis following shock as described by Mallory.[13] Precipitation of pigment in the distal convoluted and the collecting tubules was commonly observed by him between thirty-six and seventy-two hours after shock developed. Features such as necrosis and regeneration of tubules usually did not occur until the fourth or fifth day. These more advanced changes were absent in this infant. Mallory[13] added to the list of causes of lower nephron nephrosis by stating that he had observed it in a case of infantile gastroenteritis, though he did not mention the condition of the renal veins. While it seems more likely that the cause in our case, judging from the apparent age of the lesion, was related to infarction of the opposite kidney, it cannot be definitely stated that diarrheal disease alone was not responsible.

In a majority of reported cases of venous thrombosis in infancy there has been infection elsewhere in addition to that of the intestinal tract, although pathogenic agents are often recovered from the latter. Each of our three patients had a concomitant infection besides diarrheal disease; in one there were infected lacerations of the scalp; in another, bronchopneumonia; in the third, acute omphalitis. Thus, there was a potential source of bacterial toxins present in each. Pneumonia, pharyngitis, otitis media, and omphalitis have been observed by others.[9] Damage to vascular walls by bacterial products is widely accepted as an important predisposing factor of thrombosis.

Pyelonephritis has been proposed[7, 14] as the initiating factor in vascular complications in the kidney, producing thrombosis of the veins and arteries by direct extension of inflammation from the renal pelvis. Seldom, however, have bacteria been isolated from these infarcted kidneys.[15] Morison's nine cases of thrombosis of intrarenal veins with renal infarction were not associated with pyelonephritis,[5] nor was renal infection observed in our cases. There was no inflammation of renal pelves, ureters, or urinary bladder. The presence of occasional inflammatory cells in the walls of thrombosed vessels (Fig. 5) in the vicinity of infarcted areas is entirely consistent with the mild degree of inflammation usually associated with thrombotic lesions of any cause, and when found alone is not a criterion of pyelonephritis. Renal infection cannot be considered a prominent feature of the condition.

The occurrence of hemorrhage, frequently perirenal, following renal infarction has led to the assumption that a hemorrhagic tendency exists in these

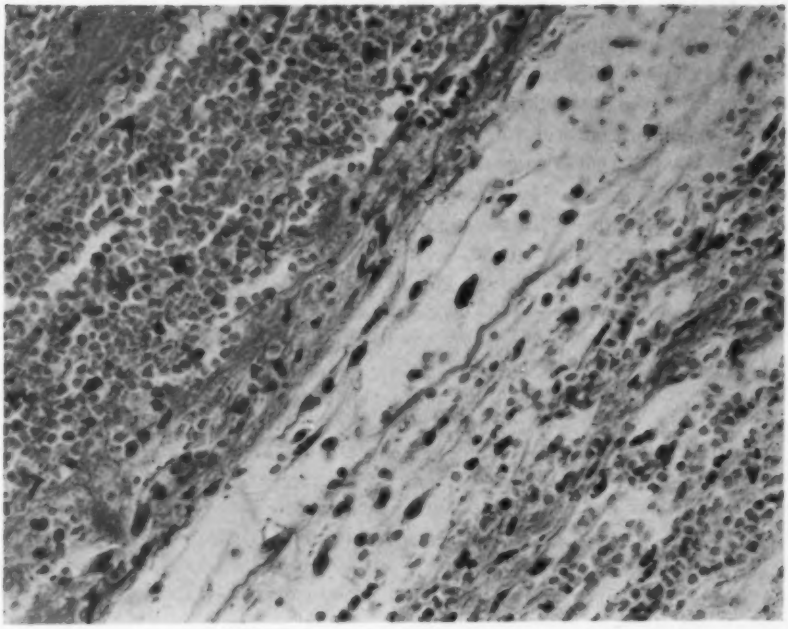


Fig. 5.—Case 3. Occasional polymorphonuclear leucocytes in wall of thrombosed right renal vein.

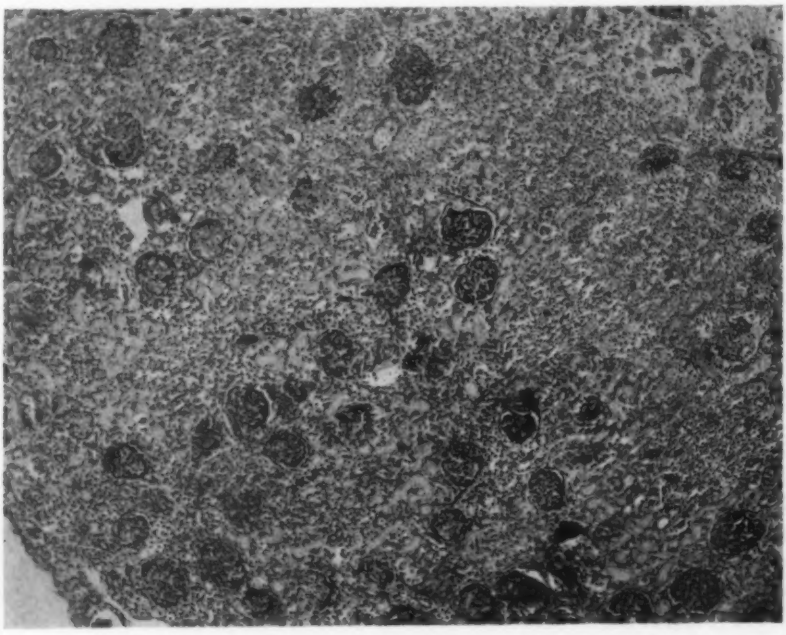


Fig. 6.—Case 3. Intact subcapsular glomeruli.

infants. There was marked perirenal hemorrhage in Case 2 and hemorrhage of the renal capsule in Case 3. This localization, plus the absence of hemorrhage in the intestinal tract, led to the belief that this perirenal hemorrhage was on a mechanical basis rather than a hemorrhagic, and was secondary to occlusion of the renal veins. It may be pointed out that perirenal hemorrhage is especially common when renal vein thrombosis occurs in adults in whom there is no question of hemorrhagic disease. There is no evidence that these infants are more susceptible to generalized hemorrhagic phenomena than are normal infants. Hypoprothrombinemia has been reported,[7] but this is characteristic of the neonatal period and cannot be considered a specific cause of hemorrhage in renal infarction. While there was a slight degree of subarachnoid hemorrhage in Case 1, and of interstitial hemorrhage of the thymus in Case 2, these are lesions frequently observed in neonatal death from any cause and may be manifestations either of birth trauma or of anoxemia.[16]

The usual gross picture of a kidney, the seat of venous thrombosis, is one of dark red discoloration mottled with foci of pale gray. Abeshouse[8] stated that red infarcts of the kidney are characteristic of venous occlusion, while pale infarcts are usually the result of arterial occlusion. Other reports do not verify this statement,[6] and there is no reason to believe that the pale foci so commonly observed in these kidneys are the result of other than the rapid decolorization undergone by an infarct in a highly vascular organ. The preservation of glomeruli and tubules in foci immediately beneath the capsule of an otherwise completely necrotic kidney (Fig. 6) indicates that some circulation is maintained through collateral channels in the capsule.[5]

DIAGNOSIS

Whereas the symptomatology of renal infarction in adults may be quite distinct with acute onset of severe flank pain followed by progressive hematuria and the appearance of a palpable flank mass, in infancy these symptoms are usually obscured by the simultaneous presence of dehydration, acidosis, and shock.

The syndrome of thrombosis of the renal vein in infancy appears to be preceded by a progressive severe diarrhea, often in the neonatal period, frequently complicated by severe dehydration, metabolic acidosis, and shock. After a period of from one to four days, gross or microscopic hematuria occurs, associated with albuminuria and often with oliguria or anuria. Simultaneously with the onset of hematuria, a characteristically firm, smooth, moderately tender mass becomes palpable in the region of one or both kidneys. The mass may subsequently enlarge and, if palpable bilaterally, is of gravest prognostic significance. With the persistence of diarrhea, dehydration, hematuria, and anuria if present, a state of collapse develops which is followed shortly by death.

The characteristic urinary findings consist of gross or microscopic hematuria, or hemoglobinuria, with varying degrees of associated pyuria, cylindruria, and albuminuria.

Campbell[7] has stressed the importance of both excretory and retrograde urographic studies. Melick and Vitt,[17] in emphasizing the necessity for early

urographic studies in these patients, pointed out that the earliest pathologic changes in the kidneys following thrombosis of the renal vein consist of parenchymal swelling and edema and that these changes will prevent the appearance of dye in the renal pelvis if retrograde studies are deferred. The characteristic findings of excretory urography consist of absence of visualization of dye in the urinary tract associated with moderate enlargement and indistinctness of the renal shadows on the involved side. In normal newborn infants, however, visualization of the urinary tract by intravenous pyelography may be difficult due to inadequacy of renal concentrating function.

Retrograde urographic studies performed promptly when thrombosis of a renal vein is suspected may enable the surgeon to determine whether the renal involvement is unilateral or bilateral. Early retrograde urography shows incomplete or irregular filling of the renal pelvis on the affected side due to the parenchymal degeneration which follows vascular obstruction. If the retrograde studies are deferred until late in the course, irregular diffusion of the dye throughout the renal tissue often will be seen, suggesting pyelovenous backflow due to necrosis.[7]

In summary, the diagnosis of thrombosis of the renal vein with infarct of the kidney in infancy is based on the history of onset of hematuria in an infant usually associated with severe diarrhea, followed by the appearance of unilateral or bilateral flank masses. The diagnosis may be confirmed by the presence of characteristic findings in the retrograde urographic studies.

TREATMENT

Abeshouse[8] emphasizes the fact that the greatest hope for recovery in cases of thrombosis of the renal vein is prompt surgical intervention with nephrectomy following an early diagnosis. However, he points out that extension of the thrombus to the inferior vena cava or to the opposite renal vein may develop following surgery. Because of this, he emphasizes the necessity for precise examination and palpation of the renal vein at operation to determine the location and extent of the thrombotic process in the venous pedicle. The importance of ligating the renal vein distal to the central extension of the thrombus is apparent.

The management of these patients is twofold, for the adequacy of the preoperative and postoperative supportive therapy must largely determine the success of the operative procedure. Of primary importance preoperatively is the correction of the shock, dehydration, metabolic acidosis, oliguria or anuria, and the electrolyte and protein depletion so frequently observed.

In addition to the routine postoperative assurance of adequate fluid, electrolyte, caloric, and protein intake, the greatest postoperative problem would appear to be the prevention of the development of further thrombotic lesions. There have been no reports evaluating the significance of a possible prothrombin abnormality predisposing to thrombosis of the renal vein, with hemorrhagic renal infarction. It is to be noted that in each of the three cases presented, there were thrombi present in organs other than the kidneys. The encouraging

results obtained with heparin and Dicumarol, in the prevention and treatment of venous thrombosis at other sites, suggest that anticoagulant therapy may be beneficial in the postoperative management of renal vein thrombosis.

SUMMARY

1. Three cases of thrombosis of the renal vein with infarction of the kidney in newborn infants as a complication of diarrhea are presented.

2. This is not an uncommon autopsy finding, and should be suspected clinically when dehydration, shock, hematuria, or anuria, and a tender mass in one or both flanks are associated with diarrhea in the neonatal period.

3. The condition is rapidly fatal. Prompt surgical intervention and postoperative anticoagulant therapy is at present the treatment of choice.

REFERENCES

1. Rayer, P. F. O.: Traité des Maladies des Reins, Paris, 1837-1841, J. B. Baillière.
2. Pollak, O.: Ueber Nierenblutung im Säuglingsalter eine Nachkrankheit des Darmkatarrhes, Wien. med. Presse **12**: 457, 1871.
3. Hutinel, V.: Les Maladies des Enfants, Paris, 1909, Asselin Houzeau.
4. Oppenheim, E.: Ueber den Haemorrhagischen Niereninfarkt der Säulinge, Ztschr. f. Kinderk. **26**: 192, 1920.
5. Morison, J. E.: Renal Venous Thrombosis and Infarction in the Newborn, Arch. Dis. Childhood **20**: 129, 1945.
6. Behr, E.: Les Altérations Morphologiques du Rein dans la Thrombose de la Veine Renale, Arch. internat. de méd. expér. **13**: 273, 1938.
7. Campbell, M. F., and Matthews, W. F.: Renal Thrombosis in Infancy, J. PEDIAT. **20**: 604, 1942.
8. Abeshouse, B. S.: Thrombosis and Thrombophlebitis of Renal Veins, Urol. and Cutan. Rev. **49**: 661, 1945.
9. Barenberg, L. H., Greenstein, N. M., Levy, W., and Rosenbluth, S. B.: Renal Thrombosis With Infarction Complicating Diarrhea of the Newborn, Am. J. Dis. Child. **62**: 362, 1941.
10. Smith, C. A.: The Physiology of the Newborn Infant, Springfield, Ill., 1945, Charles C Thomas.
11. Landis, E. M.: Capillary Pressure and Capillary Permeability, Physiol Rev. **14**: 404, 1934.
12. Woodbury, R. A., Robinow, M., and Hamilton, W. F.: Blood Pressure Studies on Infants, Am. J. Physiol. **122**: 472, 1938.
13. Mallory, T. B.: Hemoglobinuric Nephrosis in Traumatic Shock, Am. J. Clin. Path. **17**: 427, 1947.
14. Schröder, K.: Über die Thrombose der Nierenvenen, Virchows Arch. f. path. Anat. **262**: 634, 1926.
15. Finkelstein, H.: Lehrbuch der Säuglingskrankheiten, Berlin, 1921, Julius Springer, p. 758.
16. Potter, E. L., and Adair, F. L.: Fetal and Neonatal Death, Chicago, 1940, University of Chicago Press.
17. Melick, W. F., and Vitt, A. E.: Thrombosis of the Renal Vein, J. Urology **51**: 587-596, 1944.

A TABLE UNIT FOR FLUOROSCOPIC EXAMINATION OF INFANTS

MARTIN M. MALINER, M.D.
BROOKLYN, N. Y.

THE problem of satisfactorily examining the chest in infants under the fluoroscope has never been properly solved. In spite of many advances in the construction of radiological machines, the physician has been at a loss in the matter of properly supporting infants and smaller children while being examined. For older children and adults in chest examinations the erect is the position of choice. Infants are either held in the arms of the parent or are placed in the horizontal position on the x-ray table for a very unsatisfactory and distorted examination.

The author, in his search for a means of holding infants for cardiological fluoroscopic examinations, has devised a table unit which has proved to be of invaluable assistance in properly supporting smaller children. With this setup (see Fig. 1) no outside help is required. The table unit is very secure and is an excellent tool for use in the office as well as in the clinic.

The unit is an inexpensive item comprised of a standard height wooden table 29 inches from the floor. In the center of the table top is a punch hole into which a dolly of wood fits from under the center of the removable seat top. This serves as a fulcrum and permits rotation of the seat top into various positions. The standard table is 13 inches wide and 22 inches long. The removable seat top is 20 inches long, 9 inches wide, and 7 inches high. The arm holders are each 16 inches high, 8 inches long, and 6 inches wide. There is a double one-half inch cutout in the floor of each arm holder to permit extension of each holder to as much as 5 inches on each side. The slides are held in place by a bolt and thumb screw. This arrangement permits accommodation to any size infant. The arms of the holder are cut out 2½ inches to allow the infant to sit comfortably with the arms of the child extended through the grooves. After the patient is seated the arms of the holder are approximated, the thumb screw tightened, and the infant is then held snugly. Extending from the floor of the removable seat top is a rotating arm, under which is a dolly which fits into a series of holes set in a circular manner. This allows for rotation of the infant to any position with security, and the physician is able to examine his patient in the three standard positions, i.e., anterior posterior, left anterior oblique, and right anterior oblique. The doctor is able to sit down and be assured of a cooperative child. By taking off the removable table top, older children may be seated and be examined on the standard table.

SUMMARY

A table unit is presented for fluoroscopic examination of infants and smaller children. By means of this unit the patient may be examined in the

From the Pediatric Department of the Post Graduate Unit of University Hospital, New York University Bellevue Medical Center.

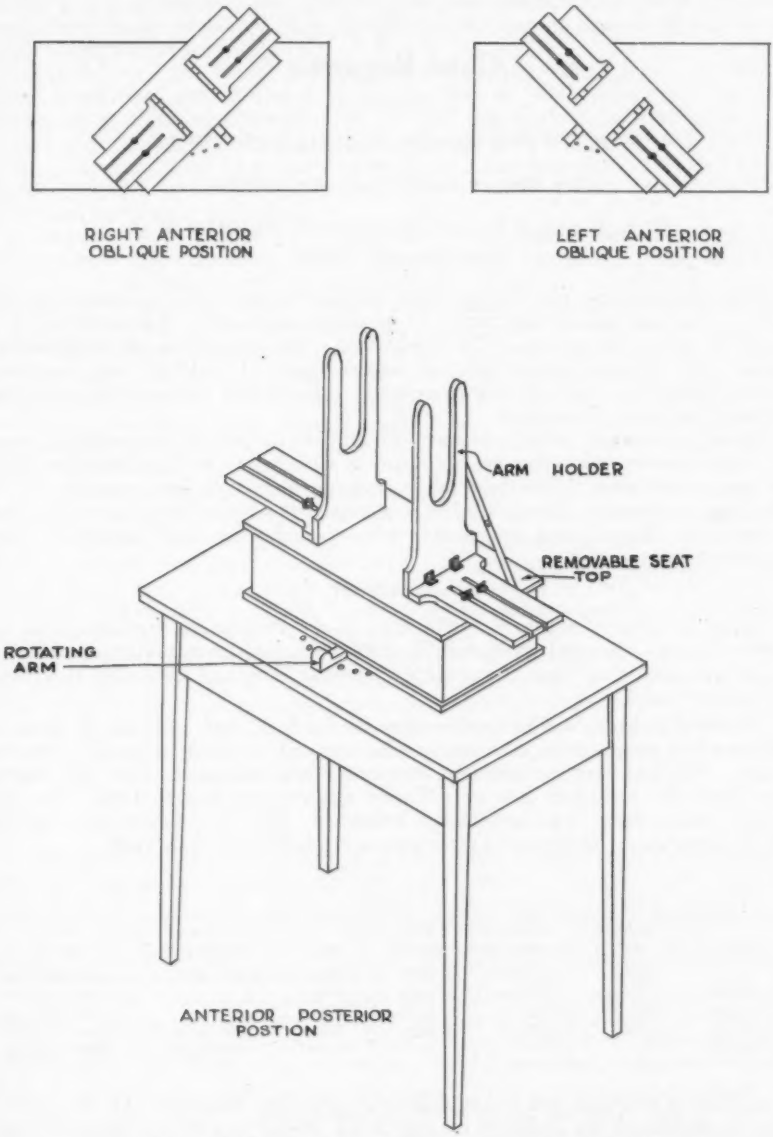


Fig. 1.—Table unit for fluoroscopic examination of infants.

erect position. This unit is adjustable so that the patient may be rotated to any position with security, without assistance, and with comfort to the examining physician.

Case Reports

CONGESTIVE HEART FAILURE IN UTERO

Case Report With Necropsy Findings

G. E. Rader, M.D., and Raymond D. Goodman, M.D.
Los Angeles, Calif.

CASE reports merit publication when they are of special or unusual interest. It is the purpose of this paper to present such a case. The occurrence of congestive heart failure in adults is common. Its occurrence in progressively younger individuals is proportionately less common. It is likely that the occurrence of congestive heart failure in newborn infants may be more frequent than has been previously recognized.

When a newborn infant presents the clinical picture of generalized edema, one must consider congestive heart failure in addition to erythroblastosis fetalis, sclerema, scleredema, hypoproteinemia, sodium retention, and syphilis in the differential diagnosis. The following case report is illustrative of an infant who showed both clinical and necropsy evidence of having had congestive heart failure in utero.

CASE REPORT

Baby A., aged 3 hours, was admitted to the Premature Station of the Los Angeles County Hospital on March 24, 1949. The pertinent maternal and birth history was obtained from the private physician who had delivered the infant at a nearby hospital.

Prenatal History.—The mother was 23 years of age, gravida iii, para iii. Two previous pregnancies were uncomplicated and resulted in normal full-term infants. Medical care for the last pregnancy was sought on Feb. 17, 1949, at which time the expected date of delivery was set for May 9, 1949. The first medical examination was essentially negative. The fetal heart rate was 140 beats per minute. Subsequent examinations are summarized in Table I.

Table I

Date	Weight (lb.)	Blood Pressure	Ankle Edema	Urine	Fetal Heart Rate	Diet
3/ 7/49	182	148/86	2 plus	Neg.	144/min.	Low sodium
3/11/49	177½	135/80	1 plus	Neg.	—	Low sodium
3/14/49	181	136/90	3 plus	Neg.	—	Low sodium
3/21/49	182½	127/76	1 plus	Neg.	160/min.	Low sodium
3/24/49	—	—	—	—	160/min.	Low sodium

In addition a serologic test for syphilis was negative, blood was AB Rh positive, and a scout film of the abdomen on March 31, 1949, revealed one fetus and polyhydramnios.

Birth History.—Labor began spontaneously on March 24, 1949, and lasted approximately five hours. Delivery was spontaneous and no instruments were used. Analgesia consisted of 10 grains of Delvinal* (sodium vinbarbital) and

From the Departments of Pediatrics and Pathology of the Los Angeles County Hospital.
*A product of Sharp & Dohme, Inc.

1/200 grain of scopolamine. Drop ether was administered during the second and third stages of labor. Ten milligrams of vitamin K were given intramuscularly during the first stage.

At delivery the infant had generalized pitting edema involving the scalp, face, trunk, and extremities plus massive ascites. Breathing was labored and moderate cyanosis was present. In view of the marked respiratory and circulatory distress, an immediate abdominal paracentesis was performed. More than 250 c.c. of peritoneal fluid were drained and there was immediate improvement in the infant's breathing and color. The infant was then transferred to the Los Angeles County Hospital.

Physical Examination.—On admission the physical examination revealed an active premature Caucasian male infant weighing 4 pounds, 10 ounces. He had a weak cry and slight generalized cyanosis. Moderate generalized edema and ascites were present. There were small bilateral cephalhematomas over the occipitoparietal areas. The lungs were clear, breath sounds being heard in all lung fields, and no râles were detected. The heart was not enlarged to palpation. Heart tones were of fair quality and no murmurs were heard. The abdomen was protuberant, soft, flabby, and edematous. Clear yellow fluid exuded through a small transverse incision below the umbilicus. The liver was palpable 2 finger-breadths below the right costal margin and the tip of the spleen was just palpable below the left costal border.

Laboratory Findings.—Hemoglobin was 20.0 Gm. per 100 c.c.; twelve hours later the hemoglobin was 21.0 Gm. per 100 c.c. White blood count was 18,000 per cubic millimeter with 80 per cent polymorphonuclear leucocytes and only a rare nucleated red blood cell seen on the blood smear. Urine analysis: negative, Wassermann and Kahn: negative, blood: Rh positive, Coombs test: negative. Albumin/globulin ratio: 2.8/1.7 with a total plasma protein of 4.6 Gm. per 100 c.c.

Course.—The infant was placed in a heated bed and given oxygen, vitamin K, penicillin, pharyngeal suction, caffeine, and whiffs of spirits of ammonia. The infant's condition remained unchanged for approximately thirty-six hours, during which time he urinated four times but did not have any bowel movements. He then began to have recurrent episodes of cyanosis with periods of apnea and expired on March 25, 1949, after forty-six hours of life.

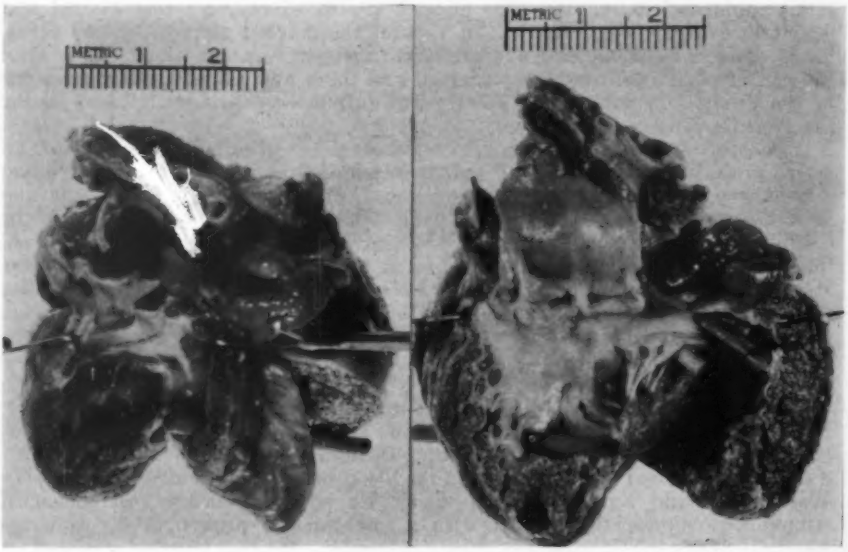
NECROPSY FINDINGS

External.—The body is that of a premature Caucasian male infant weighing 2.2 kilograms and measuring 45 cm. in length. Bilateral cephalhematomas measuring 3 × 3 × 4 cm. are present over the superior parietal surfaces. The abdomen is markedly distended and a fluid wave can be demonstrated. A one centimeter transverse incision lies in the midline just below the umbilicus. The umbilical cord reveals no abnormalities. There is no jaundice.

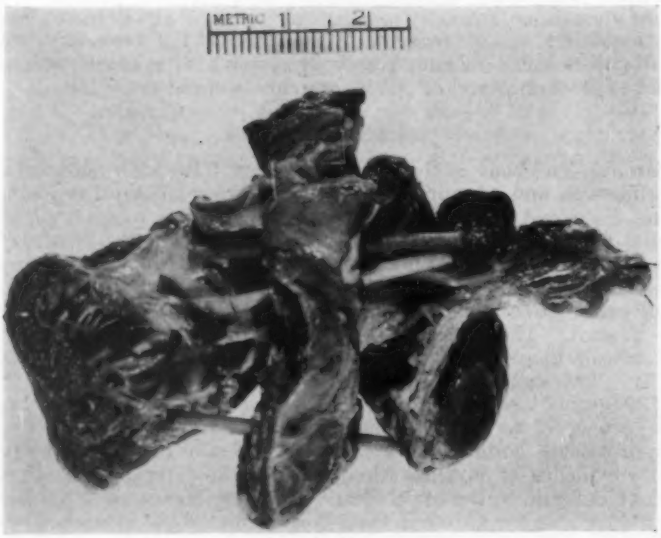
Skull and Central Nervous System.—Bilateral encapsulated cephalhematomas are present. There are no skull fractures. Examination of the cranial contents reveals bilateral nonencapsulated accumulations of liquid bloody fluid subdurally. Two small tears are present in the tentorium cerebelli. The brain weighs 230 grams. Neuropathologic report of the formalin-fixed brain states that the pattern of the convolutions of the cerebral cortex is that of an infant whose approximate gestation is six months. Sections through the brain show very little evidence of myelinization, even in the internal capsule, and practically none is found in the brain stem. These findings suggest a greater degree of prematurity than the apparent chronological age would indicate.

Respiratory System.—No pleural fluid is present. The left lung weighs 16.5 grams and the right lung weighs 19.5 grams. Both lungs are pink and float in water. Tracheobronchial trees are clear. Cut surfaces show no gross abnormalities.

Cardiovascular System.—The pericardial sac is distended by approximately 10 c.c. of clear serous fluid. The heart weighs 24.0 grams. The usual four cardiac chambers are present. The right atrium is moderately dilated. The right



A. *B.*



C.

Fig. 1.—*A.* Pulmonic valve is stretched and distorted between traction pins. *B.* Aortic valve shown for comparison with pulmonic valve. Note wooden probe in upper of two 1-V septal defects. *C.* From above downward, wooden probes are placed in the patent foramen ovale, patent septum primum, and the uppermost 1-V septal defect.

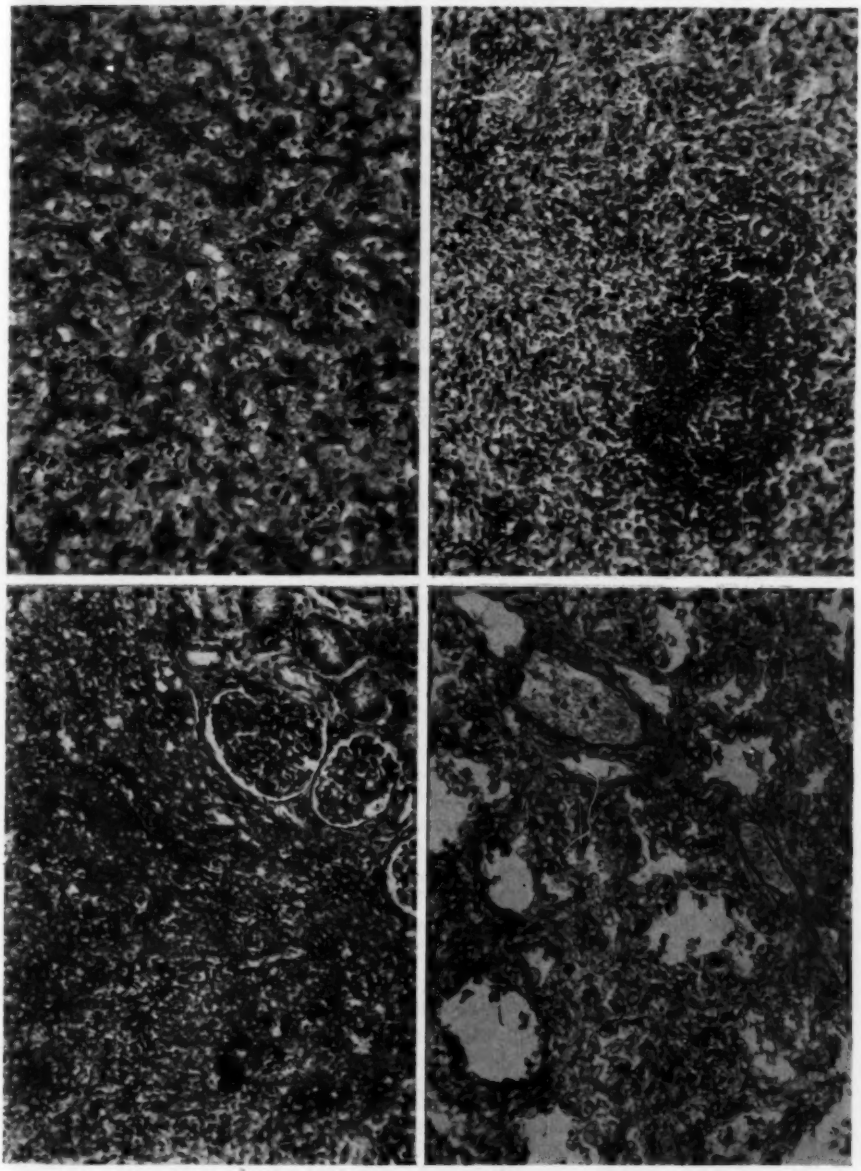


Fig. 2.—Photomicrographs magnified (×150) showing chronic passive congestion of *A*, the liver, *B*, the spleen, and *C*, the kidney, with relative sparing of *D*, the lung.

ventricle is 3 mm. in thickness and the left ventricle is 5-6 mm. in thickness. There is a patent interatrial defect of the septum primum as well as a patent foramen ovale. Two very small interventricular septal defects are also present. The endocardium is smooth. The pulmonary valve is markedly stenotic, the cardiac valve measurements being as follows: tricuspid, 31 mm.; pulmonic, 11 mm.; mitral, 40 mm.; and aortic 23 mm. The pulmonic stenosis is not associated with any gross abnormality of the semilunar cusps. The ductus arteriosus is patent. No malposition of the great vessels is present. The cut surfaces of the myocardium show no gross pathologic changes.

Digestive System.—The peritoneal cavity is filled with straw-colored fluid. The esophagus, stomach, and small intestine reveal no abnormality. The ascending and transverse colon are dilated secondary to a partial obstruction of the transverse colon by a thin congenital band. The remainder of the colon and rectum are normal. The pancreas shows no abnormality. The liver extends below the right costal margin and weighs 110 grams. It is dark brownish-red. The extrahepatic biliary ducts are patent. The gall bladder is normal. The portal system reveals no pathologic change.

Spleen and Lymphatics.—The spleen extends below the left costal margin and weighs 17 grams. It is dark purplish-red and firm. No enlarged lymph nodes are found.

Genitourinary System.—The kidneys are of equal size and together they weigh 20.0 grams. Their capsules strip with ease, revealing smooth surfaces with fetal lobulation. Cut surfaces show no gross abnormality. The renal pelves, ureters, and urinary bladder show no abnormality. The scrotum is edematous. The testes appear normal.

Endocrine System.—The pituitary gland reveals no abnormality. The thymus does not constrict nor compress any of the great vessels or structures of the neck. The thyroid gland is not enlarged. The adrenals appear normal. They have a yellow cortex and a brownish-red medulla.

MICROSCOPIC EXAMINATION

Lung.—Patchy areas of edema and atelectasis, and some pigment-filled macrophages were found.

Heart.—No inflammatory or degenerative changes were noted.

Liver.—Severe passive congestion and Kupffer cells filled with pigment were seen.

Spleen.—Severe passive congestion was apparent. Distinct and numerous lymph follicles were seen.

Kidney.—Marked congestion of the capillaries was seen.

Adrenal.—Passive congestion of medulla was apparent. The cortex was rich in lipoid.

Thymus.—Active hematopoesis was noted.

Pancreas.—Many normal-appearing islets were seen. Acinar tissue was normal.

DISCUSSION

The clinical and pathologic findings in this case are consistent with the diagnosis of congestive heart failure. The predominance of passive congestion in the abdominal viscera, extremities, and pericardium in contrast to the relative sparing of the lungs suggests that the primary mechanism was one of right heart failure. This coincides with the anatomic lesion of pulmonic stenosis. It is unlikely that the septal defects contributed to the development of the congestive state. If anything, it is very probable that life could not be long sus-

tained in the absence of these defects, for they provided a right to left shunt to circumvent the obstruction to the pulmonary flow caused by the pulmonary stenosis.

This raises the question of how much blood flows through the pulmonary artery in the normal fetus as compared with the quantitative flow through the foramen ovale. This question is unsettled and until the work of Patten[1, 2] the concept we are proposing would have been untenable. However, Patten estimates from comparative vessel measurements that 75 per cent of the fetal circulation passes out of the right ventricle via the pulmonary artery and only 25 per cent passes through the foramen ovale. This is indirect evidence of the great strain thrown upon the right heart in the presence of marked pulmonary stenosis.

More objective evidence is apparent from a study of the organ weights. In Table II, listed in columns one and three, are the organ weights in relation to body weight taken from the studies of Potter and Adair.[3] The center column contains the organ weights of this infant. It can be seen that the lungs weigh far less by comparison than do the abdominal organs. The lung weight depends greatly upon its fluid and blood content, and it is obvious that a pulmonary stenosis would deprive the lungs of blood. On the other hand, the greater than normal weight of the liver and spleen seems to be due to the passive congestion of these organs.

TABLE II

BODY WEIGHT (GM.)	2,006*	2,200†	2,508*
Heart (Gm.)	14.5	24	17.9
Lungs (Gm.)	44.2	30	49.5
Liver (Gm.)	87.9	110	105.8
Spleen (Gm.)	5.8	17	7.6
Kidneys (Gm.)	18.3	20	21.1
Brain (Gm.)	289.2	230	332.6

*Arithmetic mean weights in relation to mean body weight.
†Actual weights in this case report.

The other causes of generalized edema of the newborn infants mentioned in the introductory paragraphs are not seriously considered in this case. Erythroblastosis fetalis can be excluded by the finding of an Rh-positive mother, an Rh-positive infant, a negative Coombs test, plus the absence of peripheral circulating erythroblasts, anemia, and jaundice. Sclerema neonatorum is characterized by intense induration of the subcutaneous tissues. This obviously was not present in this instance. Scleredema is a severe form of edema which is of the hard, brawny type. It differs somewhat from sclerema in that the latter usually has circumscribed skin lesions. Scleredema was likewise not apparent in this case. Could this have been due to hypoproteinemia? Comparatively few studies have been made of the serum protein levels in premature infants but many have been made of the levels of the full-term infant. These studies show considerable variation in the average figures for the total protein and for the albumin and globulin levels. According to Dunham,[4] the average level of serum protein for newborn premature infants is frequently quoted around 4.55 Gm. per 100 c.c. This compares favorably with the value of 4.6 Gm. per 100 c.c. obtained in this infant. The dietary regime of the mother had been adequate during the pregnancy with the exception of the low sodium intake during the last two weeks before delivery. Electrolyte determinations were not made on the infant's blood or urine. However, in view of the mother's low sodium intake, the theory of edema due to sodium retention by the fetus is hardly tenable. The last consideration in our differential diagnosis is syphilis. Negative serologic tests were obtained from both the mother and infant. Moreover, there was no gross or microscopic pathologic evidence suggestive of syphilis. The evidence

strongly suggests that the clinical picture was one of congestive heart failure, that it occurred in utero, and that the chief congenital defect was pulmonary stenosis.

SUMMARY

The case of a premature infant who developed congestive heart failure in utero has been presented. Other causes of generalized edema in newborn infants have been briefly discussed. It is suggested that some of the "idiopathic" edematous states seen in newborn infants may represent congestive heart failure that is unrecognized.

REFERENCES

1. Patten, B. M.: The Circulatory System; Embryological, in Growth and Development; Part 2: Anatomy and Physiology. The White House Conference, New York, 1933, The D. Appleton-Century Company.
2. Patten, B. M.: Changes in the Fetal Circulation Following Birth, chap. 27, pp. 906-929, in vol. I of A. H. Curtis' Obstetrics and Gynecology, Philadelphia and London, 1933, W. B. Saunders Company.
3. Potter, Edith L., and Adair, Fred L.: Fetal and Neonatal Death, Chicago, 1949, University of Chicago Press.
4. Dunham, Ethel C.: Premature Infants, Federal Security Agency, Social Security Administration, 1949.

FRIEDLÄNDER'S PNEUMONIA WITH MULTIPLE LUNG ABSCESSES: RECOVERY FOLLOWING THE USE OF STREPTOMYCIN AND AUREOMYCIN

SEYMOUR GRUBER, M.D., RICHARD D. TURIN, M.D., S. DAVID STERNBERG, M.D., AND HENRY RASCOFF, M.D.
BROOKLYN, N. Y.

PNEUMONIA caused by the Friedländer's bacillus (*Klebsiella pneumoniae*) is considered to be uncommon in childhood. Bullowa[1] reports an incidence of 1.1 per cent cases of this type in a series of 4,416 cases of pneumonia. Julianelle,[2] in an extensive study of this disease, notes a similar rate of occurrence with a mortality ranging from 71 to 97 per cent. Miller, Orris, and Taus[3] in 1947 found only four previous reports of Friedländer's pneumonia in children prior to a case which they report. Grotts,[4] however, cites Kliewe as having observed an outbreak of pneumonia due to *K. pneumoniae* in 1930. Thus it is obvious that the previously reported cases in childhood are few enough to be enumerated easily.

The course of this disease may lead to early death, to chronic suppurative pulmonary disease, or to recovery in a relatively small percentage of cases. The diagnosis is made by finding the characteristic organism in the secretions of the throat or bronchopulmonary tree.[3, 4] The characteristic roentgen picture is that of diffuse patchy consolidations which coalesce. In these areas thin-walled cavities and abscesses without walls may form.

Prior to the advent of streptomycin as a therepeutic agent, there was no specific effective treatment for this form of pneumonia, and the mortality was very high. Since the use of streptomycin there have been a few reports of cases treated and cured in adults.[5, 6, 7] The first case treated in infancy was that of Miller and co-workers.[3] Their case was that of a newborn infant who ran a stormy course with no response to sulfadiazine and penicillin therapy, but who had a rapid recovery when streptomycin was started. The infant developed pulmonary cavitations but was discharged at 3 months of age as clinically cured despite the persistance of "cavities" in follow-up roentgenograms. More recently Grotts[4] presented seven cases of pneumonia in which Friedländer's bacillus was isolated as the sole or predominant organism. His patients ranged from 3 weeks to 13 months of age. All but one had an insidious onset. All failed to respond to penicillin and/or sulfadiazine. Five of the seven patients showed marked pallor or cyanosis. All had a cough, and all had some vomiting or diarrhea. There was no uniformity of the temperature curve or leucocyte count. All but two had roentgen findings of pneumonia, but none had the typical picture of abscesses and cysts. These patients showed rapid improvement with streptomycin therapy.

We are presenting another case to emphasize the value of streptomycin, and also because we believe it is the first case reported in childhood in which aureomycin was also used and in which the cavitations disappeared and the lung fields became clear.

CASE REPORT

M. W., a 13½-month-old Negro male infant, was admitted to the Beth-El Hospital with a chief complaint of high fever and cough. Ten days prior to

From the Department of Pediatrics, Beth-El Hospital, Brooklyn.

admission the infant's temperature was 104° F. A serous discharge was noted coming from the right external auditory canal and the family doctor administered an intramuscular injection of 300,000 units of penicillin. Although the infant seemed better, the temperature remained at about 101° F., and after four days penicillin via the oral route was started. There was no improvement. On the day prior to admission the temperature rose to 103.2° F. An otolaryngologist felt that there was insufficient evidence of ear pathology to account for the prolonged fever. The infant was referred to one of us (S. G.) and was hospitalized because of findings of a massive pneumonia.

Physical examination revealed a well-developed, and well-nourished, irritable, dyspneic male infant, with temperature of 102.8° F., who exhibited a marked pallor and had a hacking cough. The anterior fontanel was patent with a diameter of 1 centimeter. The tympanic membranes were slightly inflamed. The tonsils were enlarged and the oral mucosa appeared pale and boggy. Percussion of the lungs revealed dullness over the right lung area anteriorly and posteriorly and also over the left lung posteriorly. The breath sounds were markedly diminished throughout the chest. Showers of râles were heard on auscultation. The remainder of the physical examination was negative.

Fig. 1.—Admission roentgenogram showing multiple abscesses of the right upper lobe, right parietal pleural effusion, and consolidation of the right upper lobe.

The admission blood count revealed 40 per cent hemoglobin and 2.75 million red blood cells; 13,000 white blood cells with 60 per cent polymorphonuclears, one per cent eosinophiles, 37 per cent lymphocytes, and 2 per cent monocytes. Urinalyses were negative.

The infant received penicillin and sulfadiazine, and the temperature dropped to 100° for twenty-four hours; then it rose again to 103.6° F. A throat culture taken on admission was reported at this time as showing a pure culture of the Friedländer's bacillus (*K. pneumoniae*). Cultures of the nose and blood were negative. A roentgenogram of the chest showed multiple

abscesses of the right upper lobe, right parietal pleural effusion, and consolidation of the right upper lobe (Fig. 1). The infant was then started on streptomycin therapy because of these laboratory findings; the dosage was 800 mg. daily. Aureomycin therapy, in a dosage of 600 mg. daily, was started twenty-four hours later.

The temperature dropped to a normal range within twenty-four hours after streptomycin therapy was started and remained normal for the rest of the hospital stay.

The child was transfused with compatible whole blood. The hemoglobin rose to 82 per cent and the red cell count to 4.3 million.

The nose and throat cultures were negative for Friedländer's bacillus twenty-four hours after streptomycin was started, and remained so for the duration of the hospital stay.

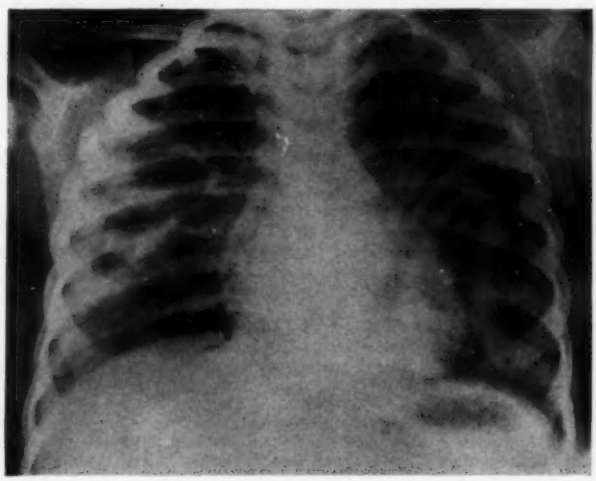


Fig. 2.—Final roentgenogram taken twenty-seven days later showing resolution of the lung pathology.

There was complete resolution of all abnormal physical findings by the seventh day of streptomycin therapy and the sixth day of aureomycin therapy. The child at this time appeared perfectly well, but serial roentgenograms indicated the continuing gravity of the patient's condition, showing at first increasing numbers of small abscess cavities and then a confluence of the cavities in the right lung. Therapy was continued and finally on the twenty-ninth hospital day a roentgenogram revealed clearing of the lung pathology (Fig. 2.). The infant was discharged after thirty-two days of hospitalization.

DISCUSSION

The discovery of the newer antibiotics has been an added impetus for more accurate bacteriological diagnosis of disease processes in order that the correct therapeutic agent may be employed. More cases of pneumonia in infancy and childhood due to *K. pneumoniae* will probably be found as a result of this trend, and more exact and effective treatment will ensue. Streptomycin, at present, appears to be the drug of choice in this disease. Aureomycin, however, has been shown experimentally and clinically to be effective in infections

caused by *K. pneumoniae*.[8] Aureomycin, if found to be as effective, may replace streptomycin because it is less toxic. The role that aureomycin played in the cure of our patient is difficult to evaluate because of the combined therapy employed. We do feel, however, that this antibiotic aided in the sterilization and closure of the cavities, a result which Miller and co-workers[3] did not achieve with streptomycin alone.

Surgical intervention was considered when the clinical condition of our patient improved, but the roentgen picture showed an enlarging cavity with fluid level and pleural effusion. It was deferred because of the remarkable well-being of the infant, and the final result obtained justified that decision.

SUMMARY

A case of pneumonia due to the Friedländer's bacillus (*K. pneumoniae*) in a 13-month-old boy is presented. There was an impressive response to streptomycin and aureomycin therapy with sterilization and closure of all cavities. Streptomycin is considered the drug of choice at present for such infections, but it is suggested that aureomycin may replace streptomycin therapy in infections due to *K. pneumoniae*.

REFERENCES

1. Perlman, E., and Bullowa, J. G. M.: Primary Bacillus Friedländer (Klebsiella Pneumoniae) Pneumonia, Arch. Int. Med. **15**: 907, 1941.
2. Julianelle, L. A.: The Pneumonia of Friedländer's Bacillus, Ann. Int. Med. **15**: 190, 1941.
3. Miller, B. W., Orris, H. W., and Taus, H. H.: Friedländer's Pneumonia in Infancy, J. PEDIAT. **31**: 521, 1947.
4. Grotts, B. F.: Pneumonia in Infancy Caused by Friedländer's Bacillus, J. PEDIAT. **34**: 174, 1949.
5. Bishop, C. A., and Rasmussen, Ruth: Klebsiella Pneumonia Treated With Streptomycin, J. A. M. A. **131**: 821, 1946.
6. Herrell, W. E., and Nichols, D. R.: The Clinical Use of Streptomycin: A study of Forty-five Cases, Proc. Staff Meet., Mayo Clin. **20**: 449, 1945.
7. Learner, N., and Minnick, W. R.: Friedländer's Pneumonia Treated With Streptomycin; Report of a Case With Prompt Recovery, Ann. Int. Med. **25**: 516, 1946.
8. Long, P. H., Schoenbach, E. B., Bliss, E. A., Chandler, C. A., and Bryer, M. S.: The Present Status of Polymyxin, Chloromycetin and Aureomycin: Experimental and Clinical: An address presented by Perrin H. Long before the American Pharmaceutical Manufacturer's Association, Dec. 7, 1948.

POTASSIUM BROMATE POISONING

Report Of A Case

Harold F. Robertson, B.S., M.D., F.A.C.P., M. William Flothow, Jr., B.S., M.D., and Martin D. Kissen, A.B., M.D.
Philadelphia, Pa.

THIS case is reported because of the unusual occurrence of potassium bromate intoxication. A survey of the recent literature reveals only a few references of a similar occurrence. Dunsky[1] reports a fatal case of a 17-month-old boy who swallowed an unknown quantity of a neutralizing solution for use on the hair after the application of a "cold wave." Thompson[2] reports the nonfatal case of a 2½-year-old male child under similar circumstances. Kitto and Dumars[3] report three nonfatal cases of potassium bromate poisoning in children as a result of the ingestion of a permanent wave neutralizing solution. These cases included two in which there was a marked initial impairment of renal function with a gradual return to normal following appropriate therapy. A third patient revealed gastric irritation as the only manifestation.

The frequent home use of "cold wave" permanents which contain potassium bromate should be called to the attention of the medical profession. They present a potential danger to children and suicidal adults. The potassium bromate is contained in the neutralizing portion of permanent "cold wave" processes. It is believed that the toxic action of bromates is similar to that of chlorates with symptoms referable to the production of gastritis and tubular degeneration of the kidneys.

E. B., a white girl aged 14 years, was admitted to the Philadelphia General Hospital on April 18, 1949. Her past medical history was noncontributory. She had ingested the neutralizer substance of a "cold wave" material six hours prior to admission. The patient suffered intermittent vomiting, per-

Table I. Blood Chemistries

DATE	4-18-49	4-19	4-20	4-21	4-22	4-23	4-24	4-25	4-27	4-28	4-29
Hemoglobin	15.4							13.7			
Carbon dioxide		40	47	60	62	68	52	58		59	58
Chlorides		504	504	509	574	532	550	714		550	568
Blood urea nitrogen		34	44	41	25	17	14	26	23	11	
Bilirubin		.77									
Potassium		4.1 meq.									
Methemoglobin		Neg.									
Sodium		148 meq.									
Bromide		None									

From the Departments of Neurology and Psychiatry of the Philadelphia General Hospital.

TABLE II.

DATE	4-19 3 P.M.	4-19 9 P.M.	4-19 MIDNIGHT	4-20 3 A.M.	4-20 7 A.M.	4-20 10 A.M.
Color	Blue	Blue-green	Blue	Blue-green	Pale blue	Pale blue
Specific Gravity	1.010	1.010	1.015	1.005	1.009	1.007
pH	7.0	6.0	7.0	6.0	Acid	Acid
Albumin	++++	++++	++++	++	++	++
Sugar	+	Trace	Trace	Trace	Trace	0
Acetone	+	+	+	+	0	0
Casts	Granular, Cellular, Hyaline +++	Granular, Cellular, Hyaline ++++	Granular 2-4	Granular –2	Granular 12-15	Granular 8-10
R. B. C.	Occasional	Occasional	Occasional	Occasional	Rare	Rare
W. B. C.	0	0	0		0	0
Epithelium	0	++	0		Many	Many
Total Quantity	⟶	⟶	750 c.c.	⟶	⟶	⟶

sistent hiccough, mild periumbilical pain, and oliguria. The physical examination was essentially normal. The psychiatric examination revealed the patient to be of a psychopathic personality type with strong suicidal drives.

This patient was administered emergency treatment consisting of gastric lavage with 2 per cent sodium bicarbonate solution; intravenous methylene blue (1 mg. per kilogram in one per cent aqueous solution); and 3 Gm. sodium thiosulfate by vein. Because of the acute gastritis, she was given nothing by mouth for the first thirty-six hours, and was maintained satisfactorily on an electrolyte balance by means of intravenous saline, glucose, and one-sixth molar solution of sodium lactate. Table I shows the blood urea nitrogen to be most elevated during the first three days of illness. The blood potassium and bromide were within normal limits and methemoglobinemia was not demonstrated. There was no severe ketosis or disturbance of sodium metabolism. Table II reveals the presence of blue-green urine due to methylene blue administration. Granular casts were frequent and albumin was 4 plus with considerable numbers of epithelial cells. It is to be noted that the patient had a complete oliguria for the first twelve hours of her illness. Her initial satisfactory urinary output was fifty hours after admission. The Addis count on May 10, 1949, was elevated above normal as follows: by volume, 320 c.c. per twelve hours; 800,000 red blood cells; 2,250,000 white blood cells; and 165,000 casts. The phenolsulfonphthalein test was 78 per cent in one hour. The urine was albumin-free after the seventh hospital day, but granular and cellular casts persisted throughout the entire hospitalization period of twenty-three days. A toxic effect is said to manifest itself on the red blood cells in the presence of chlorate and bromate poisoning. It is possible that the moderate degree of sickling and vacuolization found in the erythrocytes of this patient may be attributed to the bromate effect. This patient was discharged symptom-free on May 11, 1949. A follow-up study six weeks after discharge revealed normal clinical and urinary findings.

SUMMARY

A case of potassium bromate poisoning is reported. This type of intoxication is infrequent and results from the ingestion of the neutralizing portion of some "cold wave" permanent processes. Although the illness was not fatal in this instance, one death had been reported previously. The potential danger of this substance to children and suicidal adults is called to the attention of the medical profession.

Note: Toni Home Permanent Wave was the material used in this instance.

URINALYSES

4-20 11 P.M.	4-21	4-22	4-22	4-23	4-24	4-25	4-26	4-27
Pale blue	Green	Green	Green			Colorless	Colorless	Colorless
1.006	1.011	1.012	1.010			1.010	1.010	1.007
5.5	Acid	Acid	Acid			Acid	Acid	5.0
++	+	Trace	+			0	0	0
0	0	0	0			0	0	0
0	0	+	0			0	0	0
Granular	Granular	Cellular	Cellular			Cellular	Cellular	Cellular
Loaded	3-5	1-2	1			1-2	Occasional	Occasional
Few	Occasional	Occasional	Occasional			0	0	1-2
0	25-30	10-15	15-25			1-2	0	0
Loaded	0	Loaded	Loaded			+++	Many	Few
1,650 c.c.	1,975 c.c.	⟶	1,500	1,350	2,350	1,960	2,500	3,605

REFERENCES

1. Dunsky, Irvin: Potassium Bromate Poisoning, Am. J. Dis. Child. **74**: 730-734, 1947.
2. Thompson, H. C., and Westfall, S. W.: Potassium Bromate Poisoning: Report of a Case Due to Ingestion of a "Cold Wave" Neutralizer, J. PEDIAT. **34**: 362-364, 1949.
3. Kitto, William, and Dumars, Kenneth W.: Potassium Bromate Poisoning, J. PEDIAT. **35**: 197-200, 1949.

JUVENILE THYROTOXICOSIS TREATED WITH PROPYL THIOURACIL AND TWO SUBTOTAL THYROIDECTOMIES

LOUIS D. ALTMAN, M.D.
GREENSBURG, PA.

JUVENILE thyrotoxicosis is a rare condition and comparatively few cases have been recorded where the drug propyl thiouracil has been used in treatment. This case illustrates not only the use of propyl thiouracil, but also the performance of two subtotal thyroidectomies.

Case Report.—V. G., age 2 years, was admitted to the Westmoreland Hospital Association in Greensburg, Pa., on Oct. 11, 1947, with the chief complaint of convulsions, nervousness, and irritability.

Her mother gave the following history. V. was a normal female child at birth, weighing 6½ pounds. The only obvious abnormality that she noticed was a fullness at the root of the child's neck. At the age of 3 months, the child became slightly nervous and at times was irritable. At 6 months, the fullness at the base of the neck became more evident, and there was noticed a tendency toward restlessness, especially at night, and also her heart seemed to race. Her skin was warm, she perspired freely, and she seemed overenergetic. There was much gulping of food and stariness of the eyes became evident. The child's early development was uneventful; she had no childhood diseases. She was breast fed for approximately eighteen months. She was unable to walk until 15 months of age, and then only poorly. V.'s legs appeared very weak and she stumbled and fell often. There is no history of hyperthyroidism in the family. Conditions at home were fairly comfortable with the parents getting along well together. The child was never subjected to any bodily punishment. A younger brother is healthy.

About eight weeks before admission the child seemed to tire more easily and refused to play. Her bowel movements were pasty and gelatin-like. Her appetite remained excessive, but there was an increasing loss of weight. At times the skin appeared hot and moist.

About six weeks before admission she developed a temperature of 101° F., and complained of a mild sore throat. She became quite nervous and this was followed by a major seizure or convulsion which lasted for about one hour. During the attack the patient became doubly incontinent. Following the convulsion for about three or four days the child's heart kept racing and she perspired freely.

About four weeks before admission the child appeared to be listless and droopy and again had a major convulsion which this time lasted for approximately one-half hour. Two days before admission V. developed a temperature of 101° F., had diarrhea with some vomiting, and the heart rate became extremely fast (160 to 180).

On admission to the hospital, the child was fairly tall for her age and weighed 21 pounds. She was blonde, pale, and seemed quite emotional. She was keenly interested in her surroundings and was very friendly toward all those who visited her. The skin was very warm, moist, and flushed, nutrition was poor, and her muscles, especially those of the calves, were flabby and of poor tone. A diffuse visible fullness presented itself at the root of the neck

and moved on swallowing. There was an audible bruit on auscultation. The eyes were both prominent. There was some evidence of lid lag. A fine tremor of the outstretched fingers was present. A persistent tachycardia at rest was present, and both clinically and radiologically the heart was enlarged. There was a harsh mitral and pulmonary systolic murmur. The tip of the spleen was palpable. The throat was mildly inflamed and the tonsils enlarged. All reflexes were hyperactive.

Fig. 1.

Fig. 2.

Fig. 1.—Photograph taken before propyl thiouracil therapy and thyroidectomies.
Fig. 2.—Photograph taken ten months following second operation.

The blood picture on admission was hemoglobin 72 per cent or 10.9 Gm., red blood cells 3,840,000 per cubic millimeter of blood, white blood cells 12,400, neutrophils 18 per cent, lymphocytes 73 per cent, monocytes 9 per cent. The red blood cells showed a mild hypochromia. Blood cholesterol was 157 mg. per cent, alkaline phosphatase 4.2, acid phosphatase 1.0 Bodansky units. Sedimentation index was 10 mm. (sedimentation time 60 minutes).

Radiographic examination made of all bones showed no abnormalities or deformities, no evidence of any bone or joint absorption, destruction, or disease. The calcification of all these bones appeared to be normal and the joint surfaces, their articulations, and all the epiphyseal centers were normal. Radiograph of the skull showed no pathologic increase in the size and shape of the sella turcica.

Progress.—The patient was hospitalized for twenty-nine days, being put on propyl thiouracil therapy on the first day with the initial dose being 6 mg. four times a day, which was gradually increased to 30 mg. three times a day after meals, and 15 mg. at bedtime. As a result of this therapy the fluctuant temperature (100-101° F.) returned to normal and the pulse stabilized itself around 100. The patient's weight increased during this month from the initial 21 pounds to 35 pounds. She became quieter and less irritable. The size of the thyroid gland began to visibly decrease. The patient began to show better muscle tone with less tendency to stumbling when she walked. Radiographically the heart returned to almost normal size. There was possibly some improvement in the exophthalmus.

Progress After Discharge From the Hospital.—Propyl thiouracil therapy was reduced slowly to 15 mg. after meals and at bedtime, along with elixir phenobarbital drams ½ at 10 A.M. and 3 P.M. The patient remained in excellent health for about three weeks, and then once more developed a tendency toward nervousness, irritability, insomnia, along with frequent bowel movements. The patient developed another convulsion, and as a result was readmitted to the hospital for further treatment. At this time the patient was immediately put on Lugol's solution minim 10 three times a day, and a high caloric diet for ten days and then a bilateral subtotal thyroidectomy was performed. The patient had an uneventful recovery and remained in the hospital for two weeks.

Course at Home Following Thyroidectomy.—V. was put on elixir phenobarbital drams ½ three times a day. The child seemed to get along very well for about two weeks, and then once more began to show signs of irritability and insomnia with loss of weight. Temperature began to fluctuate (100-101° F.), especially in the afternoon. Also, the pulse became more rapid. Simultaneously with these symptoms there was a definite palpable and visible enlargement of the right lobe of the thyroid gland which moved on deglutition. The patient was again put on prophyl thiouracil therapy 50 mg. five times a day (checked with freqent blood counts). Symptoms remained pretty much the same although the patient gained 12 pounds during the ensuing eight months. She then developed a convulsion which was generalized and mainly clonic in type. This convulsion lasted about twenty-five minutes. She was readmitted for a second operation in which a right subtotal thyroidectomy was performed. Convalescence following operation was uneventful; her stay in the hospital was twenty-two days.

Course at Home Following Second Operation.—Since the second operation the patient has become quieter and much easier to manage. Her appetite has lost its voracious character and is now normal. She now weighs 40 pounds and walks well. Her skin is dry and her speech, which previously had been high pitched, infantile, and explosive, is now normal. Her hair has been transformed from a scanty to a luxuriant growth. The exophthalmus has completely disappeared, likewise the blinking of both eyes which was very evident. She is now of average or better than average height. No medications are now necessary.

The pathologic diagnosis in both instances was diffuse glandular hyperplasia of the thyroid gland.

Clinical Conference

CONFERENCE AT THE CHILDREN'S HOSPITAL OF MICHIGAN

DR. PAUL V. WOOLLEY, JR., PEDIATRICIAN-IN-CHIEF

Case 1. Idiopathic Dilatation of the Common Bile Duct (Choledochal Cyst)

DR. KARL STILLWATER (Resident in Pediatrics).—This one-year-old Negro child was admitted six days ago because of vomiting and refusal of food over a three-day period. He previously was entirely well and had grown and developed normally. His vomiting had been immediate upon eating, was not forceful, and apparently was not accompanied by pain. Neither blood nor bile had been recognized in the vomitus, which consisted of undigested food and fluid. During the two days preceding admission he had also been irritable, had slept poorly, and his abdomen had appeared to be rather distended. There had been no cough, fever, urinary complaints, or changes in bowel habits.

He was found to be in excellent nutritional state and but slightly dehydrated. When left alone he appeared quite comfortable but strenuous objection was encountered with each attempt to palpate his abdomen. Temperature, pulse, respirations, and blood pressure were all within normal range. In the abdomen after sedation a mass was delineated which was smooth, rather firm, confluent above with the liver, extended below to the umbilicus, and was lost laterally in the right flank. It extended slightly to the left of the midline and definitely did not fill the right paravertebral space. Examiners were not in agreement as to whether this mass was a solid tumor or a cystlike structure. The remainder of the abdomen was soft and bowel tones could be heard throughout; the spleen was not felt and the area of liver dullness did not appear to be increased. Laboratory data were not especially helpful since the urine showed no bile or other abnormal constituents, the hemoglobin was 11 Gm. per cent, the white blood cell count was not elevated, there was no sickling, and both tuberculin and Mazzini tests were negative. An intravenous pyelogram was the only x-ray examination even suggestive of an abnormality.

Treatment during the first two days was limited to the administration of parenteral fluids, and this was curtailed since the baby took liquids well by mouth and did not vomit. The mass did not change in size and he was quite free from symptoms during this period. Several formed stools were passed and all contained bile but no blood.

DR. JOSEPH ZBIKOWSKI (Resident in Roentgenology).—A soft tissue mass occupying the right upper quadrant and displacing the bowel downward can be seen in this film of the abdomen (Fig. 1). There are no areas of calcification and the skeletal structures are intact. Dye concentrates normally in this intravenous pyelogram and the kidneys occupy their usual positions. The

right kidney appears to be rather large but the calices are not distorted and there is no obstruction to drainage. Films of the long bones, skull, and chest are not remarkable.

Fig. 1.—Case 1. A film of the abdomen showing mass and displacement of bowel.

DR. WOOLLEY.—Before hearing from the surgeons, who operated on the third day following admission, I might say something about the management of abdominal tumors in this age group. It is important, first of all, to separate a group in which surgery is unnecessary or undesirable. This means that we must be sure the mass is not spleen, bladder, uterus, fecal impaction, or abscess. When these have been discounted we believe that diagnostic procedures might as well be kept to a minimum since the surgeon and the pathologist will have the final word anyway. Besides the usual procedures accorded all hospital patients—several urinalyses, complete blood counts, serology, and tuberculin test—it is important to have a roentgenoscopic survey of chest, skull, and long bones, and an intravenous pyelogram. The last serves many purposes: delineat-

ing the mass and establishing its relation to the kidneys, providing a fair index of renal function, and often defining the tumor as a renal neoplasm, a hydronephrotic shell, or polycystic disorder. During the period of two or three days necessary for these studies the patient is put in good preoperative condition and a reasonable interval of "observation" is fulfilled. He is then explored by a surgeon completely familiar with the aberrances likely to be encountered in the age group. At operation the pathologist should be in attendance and should share the responsibility for such decisions as are made. Please understand that this schedule does not preclude other diagnostic studies, such as examination of aspirated bone marrow or barium enema, when indicated, but it does stress the decided limitation in value of most procedures and the importance of early surgical examination and the pathologist's exactness. Numerically the two important tumors at this age are the embryoma of Wilms and the neuroblastomas, but it is no rarity to encounter something entirely different. I cannot, however, recall an instance in recent years, when harm has been done through an exploratory laparotomy or when the absence of more extensive preoperative study has been regretted; this is largely a tribute to the experience, conservatism, and judgment of our surgeons and pathologist.

Dr. Jack Hertzler (Resident in Surgery).—When Dr. Clarence Maguire undertook to explore this baby, it was not clear what might be encountered except that a neuroblastoma was favored over a Wilms' tumor since the mass was not prominent in the flank and since no distortion of the kidney was present by x-ray.

When the peritoneum was entered through a right paramedian incision, a cystlike mass was found immediately below the liver edge, roughly as I have illustrated on the blackboard (Fig. 2). Superficial to the main mass and lying transversely along the liver margin was a smaller cyst which was taken to be gall bladder since it connected with the larger mass by a narrow duct. Beneath the mass could be felt what appeared to be a normal kidney. Very cautious dissection was carried out, since we still were not too sure of exact relationships and, as we worked around posteriorly, another duct was encountered which extended from the cyst into the liver substance. Still a third opening was identified and this led to the duodenum in the general direction of the ampulla of Vater. The mass therefore appeared to be a cyst communicating with the liver, the gall bladder, and the duodenum; it was then a choledochal cyst or "dilatation of the common duct." Two possible courses were open to us and I still am not sure that we followed the wiser; we could merely have anastomosed the cyst to the duodenum, as recommended by Ladd and Gross,[1] or do what we finally did, remove the undilated hepatic duct from the cyst, connect it to the duodenum, and excise the entire dilated organ. Postoperatively the child has done quite well and our chief worry at the moment is that we do not know where the pancreatic duct is located, since, in following the procedure we did, it was necessary to ligate the common duct rather close to the duodenum before the cyst was removed.

A number of theories have been put forth to explain this anomaly, but none is entirely satisfactory, nor is it clear that any single mechanism is responsible. A defect in the development of the common duct wall, an abnormality in innervation, and hypertrophy due to obstruction at the duodenum have all had support on entirely theoretic grounds. It is a rather rare condition, since we can find only one earlier record here, a child, who now must be 12 years old, handled by the technique mentioned earlier as an alternative; anastomosis of the cyst to the duodenum. We are making an effort to get her back to the clinic in order to see what her subsequent course has been.

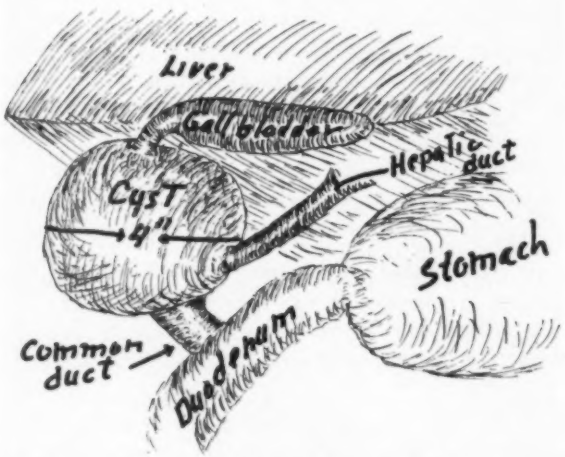


Fig. 2.—Diagram showing schematic relationships of choledochal cyst.

DR. WOOLLEY.—I am sure all of us have seen the impressive illustration of this condition in Ladd and Gross, but this is the first example I have dealt with directly. The child still has a Levine tube in place so that it should not be difficult to determine the competence of his pancreatic ducts; let us titrate the duodenal drainages for trypsin. It is interesting that this child had no earlier attacks of pain and/or a history of jaundice, either from obstruction or ascending infection; most of Gross's patients did.[2] I think this illustrates beautifully the necessity for experience and conservatism when dealing with abdominal masses during infancy; it would have been quite simple to have damaged irreparably the usable ducts had the problem been approached merely as the removal of a tumor.

FINAL NOTE

The postoperative course of this patient was uneventful and he has been free from symptoms since discharge some six months ago. While waiting for a reasonable period of follow-up before including this report in the Clinical Conferences, I had a note from a surgeon in a neighboring city requesting records of a patient on whom he had operated and found a dilatation of the common

bile duct. She had been seen in this hospital at 4 years of age because of bouts of jaundice and fever, and a mass similar to the one described above had been felt. No surgery was done because of a concomitant otitis media, and the family left Detroit soon afterward. Dr. Hertzler tells me he has also interviewed the young lady he mentioned in his discussion and that she was free from all symptoms. We therefore have had three examples of this anomaly in the past ten years.

Case 2. Obstruction of the Common Duct Due to Fibrous Tumor of the Pancreas

Dr. Mary Jane Stern (Resident in Pediatrics).—This one-year-old white girl was admitted three weeks ago because of jaundice which had first been noted three weeks earlier. At the onset there were no complaints except a gradually increasing yellowishness, first visible in the sclerae and then involving the skin. Her appetite was not disturbed, she had no pain, vomiting, or nausea. After a few days the parents noted her urine to be darker than usual and she appeared to sleep more than previously. Her physician was consulted and also could detect no essential variation from the normal except the jaundice. She was placed on a diet low in fat but adequate in simple carbohydrate and protein, supplemented with choline. During the next two weeks her condition remained unchanged except for increasing intensity of the jaundice. She ate well and lost no weight. Her temperature, recorded only periodically, ranged between normal and 100° F. and she passed from one to three light-yellow formed stools daily. On the day before admission her temperature rose to 103° F., she was irritable, and did not eat.

Nothing of assistance was learned from her past history; she consistently had been well and had received no transfusions or injections of any type. There had been no similar complaints in other members of the family nor were any instances of jaundice known to be present among neighborhood contacts. Our original examination showed just about what would be expected from the history; she was deeply jaundiced but well nourished and quite comfortable. Her temperature was 98° F. and her throat was enough injected to suggest a source for the earlier recorded elevation. Both the liver and spleen could be felt easily, but the former was not especially firm and was not tender.

A number of urine specimens were examined and all contained bile. Several blood counts were obtained showing a normal number of white blood cells and a range in hemoglobin between 10 and 11 Gm. per cent. Mazzini and tuberculin tests were negative and bile was absent from the several stools examined. Tests bearing more directly upon the cause of jaundice included normal red-cell fragility, average reticulocyte count, a urine urobilinogen positive at 1:50 dilution, and a serum bilirubin of almost 16 mg. per cent, of which 9 mg. gave a prompt and direct reaction. There was little indication of other liver damage or failure, the prothrombin time was normal on several occasions, and both thymol turbidity and cephalin flocculation tests were repeatedly nega-

tive. The serum proteins were determined as 9 Gm. per cent, with equal partition between albumin and globulin, and no bacteriologic studies were contributory.

During the three weeks here there has really been no change of any importance. She has been quite comfortable, has eaten well, maintained her weight, and has remained jaundiced. A recent reappraisal by the laboratory shows no essential change from the findings listed earlier except that her total bilirubin is now 20 mg. per cent. Last week she acquired a mild respiratory infection which lead to an elevation of temperature but during the remainder of the time she had been afebrile. Her urine is still colored by bile and her stools are still acholic.

DR. WILLIAM A. EVANS (Roentgenologist-in-Chief).—The roentgenologist is rarely of any help in these cases. A film of her abdomen shows a liver shadow which is not overly large and an absence of opaque stones or calcification. Films of her skull show normal thickness of the bones, no evidence of a hyperplastic marrow, and no pathologic defects. It was suggested that an attempt be made to give opaque dye to this patient in order to demonstrate her gall bladder but, in our experience, this is not useful. The organ is difficult to visualize in her age group, even when normal, and it is not logical to assume that when bile cannot be eliminated a dye would be concentrated.

DR. WOOLLEY.—This child is shown primarily to emphasize once more how little we know about the liver and its diseases in this age group. We can divide the causes of jaundice roughly into three groups but we must remember that these often merge into each other as the condition persists and, as a consequence, data from the laboratory become progressively more difficult of interpretation. When the jaundice is due to increased destruction of blood we should expect to find evidence of red cell regeneration with or without anemia and, so long as liver function is unimpaired, an increased urobilinogen excretion. When jaundice is due purely to obstruction in the passage of formed bile, there is no evidence early of liver damage nor of red cell loss; merely failure of bile to appear within the intestine. The majority of instances for this age group fall into the third group where the prime defect is organic or functional impairment to liver cells due to a vast array of agents, known and unknown. Here we expect, or at least hope, to find evidence of liver damage plus extrahepatic manifestation of the underlying process. The present patient was handled originally as if she had infectious hepatitis, certainly the most probable possibility. However, she has now continued for almost six weeks with no important finding other than jaundice and no evidence of liver damage. This, with the complete absence of anything to suggest increased blood destruction, leaves us theoretically with a diagnosis of jaundice due to biliary obstruction, an extremely rare possibility in a child of this age. However, as occasionally happens, we must cease to be pediatricians and assume the role of internist, hearkening back to medical school teachings that painless and asymptomatic jaundice, when progressive, is usually due to biliary obstruction at the ampulla, frequently carcinoma of the pancreas. With this girl I believe that an exploration of her liver and biliary tract is indicated, first with the idea that her troubles may be corrected and secondly, as

has been stressed here so many times before, that gross examination of the liver plus biopsy offers the greatest chance to learn more of liver disorders in childhood, especially when correlation can be had with thorough clinical study.

DR. SAMUEL BERNSTEIN (Senior Pediatrician).—I have been able to follow this child from the beginning of her complaint and originally regarded her as having infectious hepatitis. The thing that has interested me has been the complete freedom from all symptoms other than jaundice; she has played, been perfectly happy, and has not even lost weight. I do not know what she has, but I am in agreement that the next step is a laparotomy.

DR. CHARLES N. WELLER (Associate Surgeon-in-Chief).—I am willing to explore this child. She will stand the operation well and certainly the microscopic examination of liver tissue offers the best chance for diagnosis and hence treatment. Obstructive jaundice is very rare in this age group and I wonder how long such a state could exist without evidence of liver damage.

DR. WOOLLEY.—I do not know, except that we have had infants of 4 months of age come here with what you have proved to be congenital absence of the bile ducts and yet little laboratory or clinical evidence of severe damage.

DR. W. W. ZUELZER (Pathologist-in-Chief).—From the laboratory viewpoint this is obstructive jaundice. I am in favor of exploration and biopsy.

FINAL NOTE

Surgery was performed a few days after presentation. The liver was only moderately enlarged and showed no scarring or distortion. The gall bladder was markedly dilated, as was also the cystic duct, while the common duct measured at least 1 cm. in diameter. Within the head of the pancreas was an isolated, hard mass which measured roughly 4 cm. in length and 3 cm. in width and depth. It appeared to be covered on all approaches by normal pancreatic tissue, the anterior surface of which was incised in order to remove several small pieces for biopsy. A frozen section of one of these was not suggestive of malignancy, so that the mass was not removed but bypassed through the formation of the cholecystojejunostomy. A small piece of liver was removed for microscopic study before the incision was closed.

Dr. Zuelzer has reported the tumor to be histologically a benign fibroma arising from within the pancreas and probably of neurogenic origin. The liver section was compatible with biliary obstruction of moderate duration. Postoperatively this baby progressed quite well after an initial febrile period of about seventy-two hours. Bile was detected in her stools on the fourth postoperative day, and by the end of a week she was noticeably much less jaundiced. She was discharged thirteen days after surgery and was then only slightly discolored while her liver had decreased considerably in size. She has now been free from complaints for six months. Her prognosis would appear quite good although one wonders whether the tumor will increase enough in size to cause trouble, especially through impingement upon the pancreatic ducts, so that excision will become necessary later.

Case 3. Acute Hypertension, Probably Secondary to Infarctions Within a Congenitally Hypoplastic Kidney

DR. HAROLD PERKEL (Resident in Pediatrics).—This 8-year-old white boy was admitted two weeks ago because of headache, dizziness, and vomiting of three days' duration. He previously had been active, intelligent, and free from physical complaints. The remainder of the family are in good health except that the father is under treatment for mild hypertension. The onset of headache was quite sudden and was followed almost immediately by dizziness and loss of all appetite. He was given aspirin, was put to bed, and, on the following morning, seemed to be better. Toward evening the headache returned and he vomited and again complained of dizziness. The following morning he remained in bed, was drowsy, and his conversation was confused. He refused solid food but would take fluids only to vomit them immediately. This state continued until evening of the next day when he could not be aroused and when, for the first time, he experienced a generalized convulsion.

He was in coma when examined here, breathing at a rate of 14 per minute, and entirely out of touch with his surroundings. He could be aroused with difficulty but was unable to respond to questioning. A generalized convulsion occurred in the admitting room but ceased with the administration of paraldehyde rectally. No papilledema nor hemorrhage was seen in his retinas and the vessels were not described as being unusual. The blood pressure in his arms was 225/125 and no reduction of this was detected following sedation. His heart showed surprisingly little; the rate was 130 beats per minute and a soft apical murmur could be heard at the apex. There was no evidence of dilatation or of failure and the femoral pulses were easily felt, while the arterial pressure recorded in the popliteal spaces was comparable to that in the arms. The remainder of the examination and the laboratory data were not especially illuminating. The specific gravity of an initial urine specimen was 1.017 and neither red cells nor albumin were present. A specimen obtained a few hours later showed a slight trace of albumin, a specific gravity of 1.026, and still no red cells. Hemoglobin and white blood-cell count were within usual limits and both a tuberculin and Mazzini test were negative. Cerebrospinal fluid was obtained under slightly increased pressure but contained neither cells nor abnormal amounts of protein. Blood urea nitrogen and blood sugar on the night of admission were normal.

We were completely at a loss to explain this child's hypertension although most of us, initially, favored acute hemorrhagic nephritis, especially when a third urinalysis showed more albumin. During the first night in the hospital he continued in coma and had one short convulsion which was terminated with Sodium Amytal. Toward morning he regained consciousness although there had been no reduction in his blood pressure. Since nephritis was still seriously considered, he was given magnesium sulfate intramuscularly but apparently without benefit. On the second day in the hospital he was rational at times but was drowsy and complained bitterly of headache. There was no essential change during the third day and in the evening another brief convulsion was noted. On the following morning he was presented at rounds and it was agreed that

acute nephritis was no longer tenable as a diagnosis. Two procedures were recommended, a trial with benzyl dioxane, and an intravenous pyelogram. No change in blood pressure was observed with the dioxane but the pyelogram revealed an extremely small kidney on the right with no visible dye excretion. The left kidney appeared to be unimpaired. By then the patient's condition was critical; he was in coma most of the time, and twitching intermittently despite sedation. Surgery was consequently carried out immediately and on an emergency basis by Dr. Frank Bicknell. The right kidney was removed and the patient was sustained postoperatively with blood and other fluids intravenously.

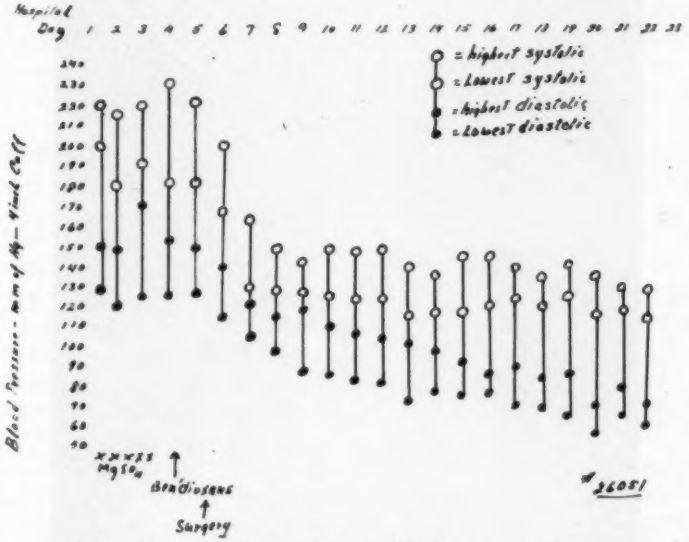


Fig. 3.—Case 3. Graph showing daily blood-pressure variations.

An appreciable fall in blood pressure was not observed until almost forty-eight hours after surgery (Fig. 3), and even then he continued to be irrational and drowsy. The following day he was awake most of the time and seemed to observe his surroundings, while on the next day he accepted fluids by mouth and talked rationally to his mother. Improvement has been quite constant since then and he now is up and around on the ward, takes an active interest in the other children, complains of no headache, and has had no drowsiness or convulsions.

Dr. Evans.—Our initial examinations included chest, skull, and abdomen. None was helpful. The heart was not enlarged nor unusual in contour and there was no pulmonary edema or congestion. It is unfortunate that the kidney shadows were not better visualized in the initial film of the abdomen. Here are the pyelograms made several days later (Fig. 4) and even in the scout film we notice that the right kidney is small. Dye leaves the left kidney promptly and this organ is not unusual in size, shape, or position.

DR. WOOLLEY.—The pediatrician is confronted with too few instances of hypertension to speak with authority on the subject, especially as in this case, when the process is acute and accounts for all of the symptoms. In theory, hypertension must be due to increased peripheral resistance to the normal or increased pressure of systole. This increase may be from a functional diminu-

Fig. 4.—Case 3. Intravenous pyelogram showing normal left kidney but no excretion of dye on the right.

tion of the vascular bed, actual organic reduction, or a combination of these elements. The causes and mechanisms of functional narrowing of vascular bed are debated in innumerable articles and tests dear to the internist but, in general, beyond the comprehension of the pediatrician, who remains rather confused by the various hormonal and nervous reflexes capable of initiating and sustaining this deviation. It is probably more profitable in this discussion merely to mention the situations of greatest importance to the pediatrician. While it can be said that in general sudden increase in intracranial content results in a compensatory vascular hypertension, this must be an extremely rare

event during childhood. When it does occur, such as following sudden subarachnoid hemorrhage, it is of a degree only to be of diagnostic interest, not to cause symptoms per se. Contrary to common belief, hypertension secondary to intracranial tumors is rare or nonexistent. Two conditions fairly common in pediatrics are characterized by markedly increased intracranial pressure and a varying degree of hypertension: acute hemorrhagic nephritis and lead poisoning. Even here a causative relationship is not well established since alternative or adjunctive explanations are obvious.

Conditions resulting in a general decrease in total renal blood flow, such as may occur in various stages of nephritis, and possibly in polycystic disease, are associated with increase in blood pressure. Acute ischemia of renal tissue commands much discussion, since many clinical problems involving unilateral kidney disorders are akin to the experimental hypertension of Goldblatt.[3] The importance of this mechanism has received considerable attention in the pediatric literature, especially as it relates to unilateral pyelonephritis, and Bell,[4] as well as Braun-Mendénez,[5] has dwelt rather thoroughly on this phase of the problem. It is important in our present state of knowledge to distinguish between generalized decrease in renal blood flow and isolated renal ischemia, since the former carries the connotation of lowered function while the latter cannot influence over-all function any more than could a nephrectomy and hence some neurogenic or humoral initiation of constriction by the ischemic tissue itself must be postulated; the renin secretion of Goldblatt, for instance. Finally, much interest of late has centered about the role of increased adrenaline secretion and hypertension such as occurs in the group of tumors commonly termed pheochromocytomas. These have been reviewed from the pediatrician's standpoint by Snyder and Vick.[6]

In the second group, hypertension due to organic impingement upon the vascular bed, the pediatrician thinks in terms of coaretation of the aorta and the various "arteritides" including periarteritis nodosa. Even with these it is fair to point out that a certain functional element may be operating; in periarteritis, for instance, the renal vascular lesions may be extensive enough to be comparable to acute hemorrhagic nephritis.

Reasoning in the present case followed rather closely this etiologic survey. Hemorrhagic nephritis was entertained initially as most probable, since it is by far the most common cause of acute severe hypertension. It must be remembered that this disease does not invariably begin with red urine or puffy eyes but may start with hypertension, convulsions, or headache, or even myocardial failure and pulmonary edema. A central accident did not appear possible once the convulsions ceased, since there were no changes in the eyes or cerebrospinal fluid and no neurological aberrances. A chronic generalized renal disease appeared unlikely without evidence of long-standing hypertension, or of retardation in growth, and in the absence of azotemia or lowered urinary specific gravity. As time passed the diagnosis of hemorrhagic nephritis became less defendable since none of the other symptoms appeared: hematuria, edema, or myocardial failure. We were thus led to the possibilities of local renal ischemia or pheochromo-

cytoma. Dr. Sibley Hoobler was kind enough to provide a supply of benzyl dioxane, and when this failed to bring about a fall in tension, we were fortunate enough to demonstrate a nonfunctioning kidney by pyelography.

DR. ZUELZER.—It is regretted that surgery was performed on an emergency basis since some of the answers were not obtained as they might have been if a more leisurely exploration had been possible. The kidney sent to us might well, from all appearances, have been removed from an 8-month-old baby; it weighed only 24 grams. It was not scarred nor infected and when opened presented normal markings and nothing to suggest an obstruction to urine flow. Microscopically the analogy to the kidney of an infant was sustained; the glomeruli were well formed but small and the tubules were rather undifferentiated and tightly packed together. Such sections of vessels as we encountered showed nothing to suggest chronic hypertension nor primary arterial disease. The only change to which we might attribute an acute elevation in blood pressure was several fresh areas of infarction in the cortex; these were pyramidal in shape with the broad bases toward the capsule. It is again too bad that we did not have the renal artery for examination, since it might explain both the infantile form of the kidney and the reason for the acute infarctions which we would like to regard either as the source of the hypertension or due to the same recent event. I could postulate that the hypoplasia of this kidney was due to an anomaly of the renal artery so that a full blood supply and hence full activity was never assumed although sufficient flow was available to maintain tissue integrity.

DR. WOOLLEY.—It is only fair to point out that we still must be rather guarded in our prognosis for this child since others have found that an immediate drop in pressure does not insure against recurrence of hypertension even though the supposed source of stimulation has been corrected. At the moment we are happy that the acute condition which threatened life has apparently abated. One very important lesson brought home to me is that although acute hemorrhagic nephritis can be used as a working diagnosis in acute hypertension, it should be abandoned earlier if other evidences do not appear; I feel that we allowed this child four days in an extremely dangerous state before undertaking a simple and obvious procedure, intravenous pyelography. It also is worth calling attention to the manner in which the heart itself stood up in the face of over a week of severe strain in contradistinction to the early failure so typical during acute hemorrhagic nephritis; it emphasizes again the importance of the myocardial lesion itself in the evolution of symptoms during the latter disease.

FINAL NOTE

Six months after presentation this child was enjoying good health and freedom from clinical symptoms. His blood pressure, however, has continued above the levels accepted as normal for this age; ranging from 140-150/90-80. He has a familial background for hypertension and we do not know his pressure prior to the acute episode, so our observation of him will continue although nothing in the way of more intensive study is contemplated at present.

Case 4. Polycystic Disease of the Kidneys

DR. MARGARET ZOLLIKER (Resident in Pediatrics).—Since 6 weeks of age this 4-month-old white baby has had what were described as jerking spells of the left side of his body. These at first were rather transitory but recently have increased in severity and frequency. He weighed 5½ pounds at birth, was difficult to resuscitate, and remained in an incubator during the first week of life. No gross deviations from normal had been noted in growth and development and, except for the jerking movements, he had been regarded as a normal infant. Four days prior to admission he was taken to one of our staff men because of irritability and increasing frequency of jerking spells. This physician palpated masses in either side of the abdomen and described the pulse as being rapid and of poor volume. During the two days immediately preceding admission the baby had been more irritable, had vomited on several occasions, and breathed more rapidly than before. There were no siblings, no stillborn infants, and the parents were young and in good health.

The child appeared to be rather pale and was moderately dyspneic, although well nourished and not dehydrated. The heart rate was elevated to almost 200 beats per minute and had a quality described as a "gallop" by several observers. No murmurs were heard and the left border of the heart did not seem extended. In the right flank was felt a series of rounded masses which extended from just below the liver to the brim of the pelvis. Not all were in agreement as to whether this was a single irregular tumor or a group of isolated enlargements. On the left side of the abdomen was a smooth oblong structure in the general area of the kidney. The liver was enlarged but the spleen could not be felt. Several people attempted to obtain accurate blood pressure records both at the time of admission and later. It was elevated with a systolic reading ranging between 180 and 160 mm. of mercury and the diastolic level always around 100 mm. There was no essential difference in pressure between the four extremities.

Our laboratory studies have not been helpful. Urinalysis included a slight trace of albumin and specific gravity of 1.010; subsequent examinations have been consistently negative. Hemoglobin was 8.3 Gm. and, while the initial white blood cell count was 28,000 per cubic millimeter, later determinations were within normal range. The blood urea nitrogen has been between 15 and 20 and the cerebrospinal fluid is normal. An electrocardiogram taken the day after admission showed a number of variations from normal for this age but nothing of diagnostic assistance. Roentgenograms will be discussed later.

While polycystic disease of the kidneys was the most likely diagnosis at admission, it was felt that a neuroblastoma, a bilateral Wilms' tumor, or even hydronephrosis due to ureteral obstruction should be excluded. However, by the second hospital day there was little doubt but what the element of cardiac failure was present. The rhythm presented a definite gallop, the pulse was of poor quality, he was dyspneic, and his liver was larger than originally noted. The baby was placed in oxygen and digitalized as rapidly as possible. He responded well to this regime so that two days later his pulse was down to 130 beats per minute and dyspnea had disappeared entirely. Intravenous pyelograms were obtained and it is planned now to attempt retrograde visualization of the kidneys.

DR. GEORGE MILLER (Resident in Roentgenology).—A film of the chest taken soon after admission shows an increase in the transverse diameter of the heart and nothing else. Films of the skull and long bones are grossly normal, and a film of the abdomen shows only soft tissue densities in the flanks. Often we are able to outline the kidneys better immediately after the injection of radiopaque material than in the flat plate, probably since the Diodrast is, at that time, actually in the parenchyma. Here in this film, taken at five minutes, we can make out a definite mass on the right but, on the left, the area of the kidney is obscured by gas in the bowel. The roentgenoscopic diagnosis of

Fig. 5.—Case 4. Intravenous pyelogram of typical polycystic kidney during infancy.

polycystic kidney classically is made on the basis of large organs into which extend long, distorted, and spidery calices. However, it is not unusual to have such poor concentration of the dye that the intravenous technique is not successful and only after retrograde injection is the diagnostic feature clear. This applies to the present patient although in a few areas I can make out what appear to be the extended and distorted calices. I would like to show this film, which is an intravenous pyelogram on an infant of about the same age seen last year (Fig. 5). It demonstrates the features we have mentioned.

DR. WOOLLEY.—I believe I mentioned, in discussing another case (Case 3), that polycystic kidney disorder provided the only cases of chronic hypertension of infancy with which I was familiar. The condition typically is seen in newborn or stillborn infants, and usually is accompanied by serious accompanying anomalies of other structures. Thereafter we do not encounter polycystic disorder with any frequency until early adult life. It is interesting to note that this is the second infant admitted here in recent months with the outstanding symptoms explainable on the basis of hypertension secondary to polycystic disorder; the present with cardiac failure and convulsions, the earlier because of retarded development which, on analysis and subsequent course, seemed best explained by marked hypertension encephalopathy. As with the child who had an infarcted hypoplastic kidney, it is necessary to fall back on a hormonal basis to explain the hypertension since this infant has relatively good over-all function but certainly could have areas of poor blood supply because of the expanding cysts. Dr. Zolliker's original differential diagnosis is quite valid in our experience. By far the most common cause of bilateral masses in the area of the kidneys of infants is the hydronephrosis secondary to urethral obstruction, while polycystic kidneys and neoplasms constitute most of the small residual. It is important to remember that when the urethra is obstructed the bladder must be either distended or hypertrophied, and this can easily be determined physically, especially if a careful rectal examination is done. We have nothing to offer this patient since surgery is obviously out of the question.

QUESTION.—Is the polycystic disease of infancy the same embryologically as that seen in adults? I have been interested in the review of the subject by Lambert,[7] whose reconstructions would indicate a glomerular and, hence, nonfunctioning lesion in the infants but with tubular dilatation in the adult.

DR. WOOLLEY.—I do not know, but it is very hard for me to see how the present patient clinically could be the same as those with a chronic renal disease of middle life, since his hypertension would preclude extended development and since his kidneys already are enlarged beyond what is seen early in adult life.

FINAL NOTE

Retrograde pyelography confirmed the diagnosis of polycystic kidneys. There has been no follow-up note on this patient.

REFERENCES

1. Ladd, William E., and Gross, Robert E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, 1941, W. B. Saunders Company.
2. Gross, R. E.: Idiopathic Dilatation of the Common Bile Duct in Children, J. PEDIAT. 3: 730-755, 1933.
3. Goldblatt, H.: Renal Origin of Hypertension, Physiol. Rev. 27: 120-165, 1947.
4. Bell, E. T.: Renal Diseases, Philadelphia, 1947, Lea and Febiger.
5. Braun-Menéndez, Eduardo, and others: Renal Hypertension. Translated by Lewis Dexter, Springleld, Ill., 1946, Charles C Thomas.
6. Snyder, C. H., and Vick, E. H.: Hypertension in Children Caused by Pheochromocytoma; Report of Three Cases and Review of Literature, Am. J. Dis. Child. 73: 581-601, 1947.
7. Lambert, P. P.: Polycystic Disease of Kidney; Review, Arch. Path. 44: 34-38, 1947.

Psychologic Aspects of Pediatrics

PSYCHIC TRAUMA OF OPERATIONS

HARRY BAKWIN, M.D.
NEW YORK, N. Y.

TONSILLECTOMY and adenoidectomy still remain the commonest operative procedures in children. Coleman,[1] an otolaryngologist, has recently called attention to some of the psychologic implications of the operation. In most instances, he points out, it represents the first admission of the child to a hospital and is often the first painful separation of the child from the home. The child, often through some ruse, is brought to the hospital where he is surrounded by strange, white-robed people. His reaction is one of terror and confusion. He is resentful at having been lied to and tricked, and he is distrustful of his parents who have deceived him and are now deserting him. The operating room and the anesthetic intensify his terror and his sense of separation.

The psychologic reaction to the operative experience varies. It is true that most children forget their disagreeable hospital stay quickly and are none the worse for their operation. But a sizable proportion show alterations in behavior, characterized principally by fears, negativism, and family antagonisms. A consequence may be fear and distrust of doctors, hospitals, anesthesia, and surgery. Coleman regards the psychic trauma which some children sustain from tonsillectomy to be as much a complication as is postoperative hemorrhage or infection.

Langford[2] has observed that severe anxiety states may be precipitated by the shock of operation. In a study of twenty children suffering from anxiety states, he found that in six of them the condition was definitely related to tonsillectomies under ether anesthesia. The child as a rule had been poorly prepared for the operation, the anesthetic, and the experience of separation from the parents. The attacks began about a month after operation and five of the six children described them as being "just like having the ether."

Levy[3] was impressed by the number of cases of fears, anxieties, and other symptoms which followed an operative procedure, most usually a tonsillectomy. Out of a group of 124 children who had had operations, twenty-five of them (20 per cent) showed residual emotional disturbances. Although postoperative symptoms occurred at all ages, they were most frequent in the one- and 2-year-old groups. Levy attributes the greater reactivity of young children to their greater dependence on home and mother, their lack of experience outside the home, and their inability to comprehend what is taking place. In addition, they are poorly equipped to handle anxiety. Unlike older children, they are unable

From the Department of Pediatrics, College of Medicine, New York University—Bellevue Medical Center, New York City.

to play out their anxiety with toys, because they do not yet possess the words, concepts, and the skill required. For the young child an operation is a raw and brutal experience the reason for which he cannot comprehend.

It is of interest that, in Levy's series, out of twenty-five children who had untoward reactions after operation, thirteen had shown no deviations from normal behavior before.

The types of postoperative reaction most frequently observed by Levy were night terrors, fears, dependency, and negativism. Most of the children with night terrors were in the younger age group (18 months of age or younger). In this group the night terrors were all of long duration, extending over months or years.

Negativistic reactions occurred principally in children 5 years old or older and consisted of such spiteful behavior against the parents as disobedience, temper tantrums, defiance, and destructive behavior.

Dependency reactions, consisting of clinging to the mother, refusing to leave her side, insisting on knowing where she is going and when she will return home, are so common after operation as to be considered normal. Occasionally, however, the manifestations may be exaggerated to an abnormal degree.

Regressive symptoms, i.e., behavior characteristic of an earlier age period, hardly ever occurred after an operative experience.

The most frequent fears in Levy's group related to darkness, doctors and nurses, and strange men. Levy attributes the fear which many children experience in the dark to fear of unknown things that may happen and to fear of being separated from the mother. This latter is directly related to the degree of dependency on the mother and, when severe, may lead to insomnia. The child who has been operated upon may also find darkness bad since "they put you to sleep and then bad things happen to you."

When a child is still suffering from the fears engendered by an operation, a second operation will usually intensify the early fears. In children in whom the fears arising from an early operation have subsided, a second operation may or may not give rise to emotional sequelae. Since it cannot be predicted how an individual child will react, it is wise to postpone a second operation, if possible, for several months after the reaction to the first operation has subsided.

To ease the plight of the child who is to be operated upon, Coleman suggests the following measures:

"1. Give the child a forthright and honest explanation of the reasons for the operation. 2. Try to avoid the element of surprise and confusion at the hospital. A recognizable picture of the hospital, the operating room, white gowned nurses and doctors should be described. 3. Explain that the purpose of anesthesia is to spare the child pain during the operation. Assurance must be given that this forced sleep is temporary and will be followed by complete awakening and survival. The ideal anesthetic is one chosen for surgical efficiency and psychic consideration. 4. Emphasize to the parents the need for constant reassurance and affection in the postoperative period. 5. Whenever possible, the doctor personally should lead the child from the mother to the operating

room. The previously established child-doctor rapport here pays dividends in the sustained security. 6. Permit overt manifestation of postoperative hostility, rather than suppress it. The psychic damage of such suppressions is fraught with subsequent danger."

Levy, in addition, suggests postponing operation, if possible, until the age of 3 years or later when the child is able to comprehend something about the meaning of the operation and is able to master his anxiety to some extent. Elective operations should be avoided in children who are unusually fearful or more than usually dependent on the mother.

Levy recommends that the anesthetic be started in the room or ward with the parents present or that the child be well sedated before going to the operating room. When the child wakes up the mother should be present.

Coleman's and Levy's very reasonable suggestions, aside from the value which they may have in preventing postoperative psychologic disturbances, are kind and humane and deserve wide application.

REFERENCES

1. Coleman, D.: Psychosomatic Aspects of Diseases of the Ear, Nose, and Throat, Laryngoscope **59**: 709, 1949.
2. Langford, W. S.: Anxiety States in Children, Am. J. Orthopsychiat. **7**: 210, 1937.
3. Levy, D. M.: Psychic Trauma of Operations, Am. J. Dis. Child. **69**: 7, 1945.

Comments on Current Literature

PROPHYLAXIS AND EARLY TREATMENT OF INFECTIONS IN THE NEWBORN INFANT

PROBLEMS peculiar to the neonatal period have received increasingly more attention in recent years. Careful studies are being carried out in an effort to solve some of these problems and to lessen the dangers which threaten the newborn infant, especially those born prematurely.

Of particular interest is the striking susceptibility of the newborn infant to infection. In a recent issue of *Acta pædiatrica*[1] Greta Muhl of the Flensburg Children's Hospital at Malmö, Sweden, reviews the experiences of her group in the prophylaxis and early treatment of neonatal infection. She points out a number of factors which contribute to the seriousness of the problem: first, there is a low natural immunity of newborn infants, especially of premature infants, which allows the infection to become generalized; second, early diagnosis is usually difficult, since clinical manifestations may be minimal, and exodus alarmingly rapid and entirely unexpected; third, the trend during the past few decades toward hospital delivery in large maternity wards, often inadequately staffed, has exposed the newborn infant to serious hazards during the first few days of life. The author believes that, in general, infections of the newborn infant are preventable and he cites the conclusions of Wallace,[2] who made a study of the causes of neonatal deaths at the Edinburgh Royal Infirmary over a three-year period from 1943 to 1946, that 25 per cent of all deaths in the neonatal period were due to infections which could have been avoided.

Since 1944, numerous cases of infection in newborn infants, particularly in premature infants, have been treated at the Flensburg Children's Hospital, and an analysis of these cases over the period from 1944 through 1948 revealed a diminution in incidence during 1945 through 1946, and a distinct rise in 1947 and 1948. The mortality rate in the latter period, 1947 through 1948, was high in spite of the availability of penicillin. From a detailed study of the records of these cases, it was apparent that where treatment was deferred until signs and symptoms of infection were definite, therapy was often ineffective. This was especially true of the premature infant. Accordingly, an effort was made to devise some means whereby neonatal infection could be detected early. The leucocyte count was found to be a helpful guide. Information concerning leucocyte counts in healthy premature infants during the neonatal period has been available for some years. Magnusson[3] showed that during the neonatal period the number of white blood corpuscles only slightly exceeded 12,000 on any one day. Numerous determinations on a large series of healthy premature infants at the Flensburg Children's Hospital verified the findings of Magnusson. On the other hand, in the majority of cases where infection was present, leucocytosis with values from 15,000 to 45,000 was common, always with a marked increase in polymorphonuclear cells. Following this lead, white blood-cell counts were made routinely on all newborn infants. In many instances this procedure revealed the presence of leucocytosis before other signs and symptoms of infection were evident, thus enabling the physician to initiate treatment early.

During the past year the following routine for premature infants has been followed at the Flensburg Children's hospital, and the results have been encouraging:

"If on admission to the hospital the children have leucocytosis with values between 15,000 and 20,000 or higher, and if they are poor feeders or lethargic without there being a suspicion of cerebral hemorrhage, or if they have loose stools, penicillin treatment is immediately commenced, with 5000-10,000 units eight times per twenty-four hours. Of late we have also employed three doses of 30,000 units each daily (e.g. 90,000 units, total). If the stools have been very disagreeable, recourse has also been had to sulfanilamide drugs in the form of sulfaguanidine or sulfathalyl. . . . If leucocytosis is present but there are no other symptoms, expectant treatment is resorted to, the blood values being followed and the child carefully examined every day and regarded as in the danger zone."

By following this routine for premature infants Muhl found that effective treatment could be started long before clear-cut signs of illness were apparent.

In 1947 Wallace[2] had initiated at the Edinburgh Royal Infirmary routine prophylactic penicillin treatment of all premature infants under 1,600 grams in weight, regardless of white-count studies. This treatment was administered for the first seven days of life, 6,000 units of the antibiotic being given orally every third hour. Muhl and her group undertook a similar study of penicillin prophylaxis, administering the antibiotic routinely, and especially to infants predisposed to infections: the asphyctic, those who had aspirated, those lethargic after cerebral injury, and to the small premature infant under 1,500 grams. The results obtained were gratifying.

While the results of these procedures designed for early treatment of neonatal infection and with a view to prophylactic prevention of infection in the premature or the newborn infant have been encouraging, Muhl is careful to emphasize the broader view of prevention of neonatal infection, especially in the case of nosocomial infection, namely, that which depends upon more adequate hospital facilities and better trained personnel:

"The most important step would therefore be to provide small wards for the premature infants and, above all, a trained permanent staff, an end that at present lies in the realm of pious wishes but which must nevertheless be pursued."

RUSSELL J. BLATTNER.

REFERENCES

1. Muhl, Greta: On Prophylactic and Early Treatment of Infections in Newborn Infants, Especially the Premature, Acta pædiat. 37: 221, 1949.
2. Wallace, H. L.: The Care of the Small Premature Infant, Edinburgh M. J. 54: 111, 1947.
3. Magnusson, H. L.: Zur Kenntnis der Blutveränderungen bei Frühgeborenen mit besonderer Rücksicht auf die Entwicklung anämischer Zustände sowie ihre Therapie und Prophylaxe, Acta pædiat. 18: 1, 1935. (Supplementum.)

News and Notes

The following were certified by the **American Board of Pediatrics** at the examination in Chicago, Ill., Dec. 9, 10, and 11, 1949.

Dr. Harry Abramson, 14 West Young St., Somerville, N. J.

Dr. Theodore Pollard Blevins, 1400 W. Jefferson Blvd., Los Angeles 7, Calif.

Dr. Stanford Borne, 32 East Mineola Ave., Valley Stream, L. I., N. Y.

Dr. Wilson Kenneth Brewer, 503 South 7th St., Springfield, Ill.

Dr. William Charles Butscher, 5919 Greene St., Philadelphia 44, Pa.

Dr. Winona Gould Campbell, 4200 East 9th Ave., Denver, Colo.

Dr. Philip J. Chastain, 103 Douglas Entrance, Coral Gables, Fla.

Dr. Egidio S. Colon-Rivera, Torre de la Vega #1300 Ave. Fernandez—Junior Stop 18½, Santurce, Puerto Rico.

Dr. Malvin Finkelstein, 2139 Hudson Blvd., Jersey City 5, N. J.

Dr. Arthur W. Fleming, 5307 Hyde Park Blvd., Chicago 15, Ill.

Dr. Mary Walker Critz Fletcher, 2905 LaBranch, Houston, Texas.

Dr. James Flett, Jr., Univ. of Colorado Medical Center, 4200 E. Ninth Ave., Denver 7, Colo.

Dr. Charles Tear Fried, 1220 Grand Concourse, Bronx 56, N. Y.

Dr. Morton Jerome Geller, 75-04 185th St., Flushing, N. Y.

Dr. Joseph E. Haddon, 532 5th St., Bremerton, Wash.

Dr. Nathan Irwin Handelman, 3618 Lexington Rd., Louisville 7, Ky.

Dr. Edward Boyd Holley, 1020 Boston Bldg., Salt Lake City, Utah.

Dr. Wilson Emery Hughes, 150 Purchase St., Fall River, Mass.

Dr. Alexander M. Iams, 110 E. Main St., Madison, Wis.

Dr. Alexander Jerome Kahn, 3120 N. Meridian St., Indianapolis, Ind.

Dr. Martin Z. Kaplan, 840 Barret Ave., Louisville, Ky.

Dr. Thomas Rogers Kirk, Burns Clinic, Petoskey, Mich.

Dr. Joseph Harry Kutch, 251-15 Union Turnpike, Bellerose 6, L. I., N. Y.

Dr. John A. Larrabee, 2455 N. W. Marshall St., Portland, Ore.

Dr. Raymond Waldron Latham, 286 Plaza Theater Bldg., Kansas City, Mo.

Dr. Milton Levitin, 683 E. Broad St., Columbus 15, Ohio.

Dr. William Alexander MacColl, 201 Securities Bldg., Seattle 1, Wash.

Dr. John Charles Martz, 325 N. Euclid, St. Louis 8, Mo.

Dr. Morris Irwin Michael, 3520 Cumberland St., N. W., Washington, D. C.

Dr. Roland E. Miller, 1625 Kossuth St., LaFayette, Ind.

Dr. Ben Mirman, 924 East Main St., Alhambra, Calif.

Dr. Irving David Mizell, 4929 W. Irving Park Rd., Chicago, Ill.

Dr. Lawrence Sewall Morse, 68 Bay State Rd., Boston, Mass.

Dr. Forrest George Moyer, 227 North 17th St., Allentown, Pa.

Dr. Harry William Orris, 244 Ocean St., Lynn, Mass.

Dr. Frederick B. Parkhurst, 500 Downing St., Denver, Colo.

Dr. Carl L. Petersilge, 13 West Church St., Newark, Ohio.

Dr. Edward F. Rabe, University of Kansas School of Medicine, Kansas City, Mo.

Dr. Charles Taylor Rumble, 700 Spring St., Macon, Ga.

Dr. Charles Jefferson Runner, 6 East Garfield Blvd., Chicago 15, Ill.

Dr. Earl S. Scott, 255 S. 17th St., Philadelphia 3, Pa.

Dr. Eugene L. Slotkowski, 5815 North Kolmar Ave., Chicago, Ill.

Dr. Bernhardt J. Statman, 849 South 12th St., Newark, N. J.

Dr. Umberto Stefano, 206 East 15th St., New York 3, N. Y.

Dr. Samuel Untracht, 50 East 78th St., New York 21, N. Y.

Dr. Edward Francis Walsh, 868 Lowry Medical Arts Bldg., St. Paul, Minn.

Dr. John A. Toomey of Cleveland, Ohio, died Jan. 1, 1950. He was born in Cleveland May 25, 1889. After graduation from John Carroll University, he studied law and was admitted to the bar in 1913. He soon changed his interests and entered Western Reserve Medical School from which he received the M.D. degree in 1919. He interned at the Cleveland City Hospital and for twenty-seven years had been the head of the contagious disease division of the hospital. Soon after graduation, he became a member of the teaching staff of the medical school and held a professorship of pediatrics for many years. He published more than 200 articles in the field of the contagious disease, many of which were published in the JOURNAL OF PEDIATRICS, and won international distinction for his research studies in the transmission and treatment of poliomyelitis. He was a member of the American Pediatric Society, the American Academy of Pediatrics, of which he was president in 1948, the American Society of Bacteriologists, and a Fellow of the A.P.H.A., A.M.A., and A.A.A.S.

Dr. Stanley H. Nichols died at his home in Asbury Park, N. J., Nov. 14, 1949. He was graduated from the University of Pennsylvania Medical School in 1910, and had been in active pediatric practice for many years. He was an outstanding leader in child health activities in his state and received the award of the Medical Society of New Jersey for his work as a member of the state board of health. He was a member of the American Academy of Pediatrics, and had taken an active part in its committee work.

Dr. Lawson Wilkins delivered the eighteenth annual series of the Benjamin Knox Rachford Lectureships on Feb. 7 and 8, 1950, in the auditorium of the Children's Hospital Clinic and Research Building, Cincinnati, Ohio. His lectures dealt with the role of hormones in regulating somatic and sexual development.

The following communication has been received from the committee for the **Sixth International Congress of Pediatrics,** Zurich, 1950:

The provisional program ("Meeting Information") of the Sixth International Congress of Pediatrics, Zurich (July 21 to 31, 1950) has been circulated to the presidents of national pediatric associations in all countries through the agencies of the American Express Co., Inc., and the foreign Diplomatic Representatives in Berne. The program is available to anybody who is interested either through the offices of the pediatric association of his own country or through the American Express Co. A short synopsis of the events that are scheduled to take place at the time of the Congress is given below:

1. Scientific and Industrial Exhibition in conjunction with an Exhibition organized by the World Health Organization which will be open to the public July 21 to 31.

2. Advanced lectures on many topics in connection with Pediatrics will be delivered in different languages during the Exhibition.

3. There will be conducted tours and demonstrations (in different languages) through a number of hospitals and welfare institutions, etc., of the town of Zurich and the neighboring districts.

4. Nurses and sisters of many countries will be invited through the International Council of Nurses to attend a Conference July 28 and 29, 1950.

Requests have been sent through the Swiss Diplomatic Service to the governments of sixty-two countries to send official representatives to the Congress. We would ask the governing bodies of all national Pediatric Societies to assist in the nomination of these delegates in order that we may have on hand the names of the officially appointed representatives before Feb. 1, 1950.

A Post Graduate Pediatric Conference will be given by the Pediatric Department at the University of Arkansas School of Medicine on March 15 and 16, 1950. This conference is sponsored by the Arkansas Medical Society and the Maternal and Child Health Division of the State Board of Health. Guest speakers will be Joseph Stokes, M.D., University of Pennsylvania, and George Piness, M.D., University of Southern California. No fees will be charged.

Book Reviews

Morbo di Cooley. G. Maggioni and A. Ascenzi, Rome, 1948, Publisher Abruzzini, 168 pages.

The authors present an accurate anatomicopathological description of two cases of patients with Cooley's anemia and discuss profusely the pathology of the disease.

They point out the hereditary character revealed by the microcythemia, which can be constantly detected in the ancestors of such patients, and classify the disease among the hemolytic familial anemias, following Frontali and in contrast with Di Guglielmo who considers Cooley's anemia as belonging to one group of conditions named by him erythremic myelosis.

Among the various factors responsible for the hyperhemolysis the authors take into consideration particularly a phenomenon of erythrophagocytosis in the bone marrow. While they have not found an increased phagocytosis in the spleen, they observed in one of their patients the presence in the bone marrow of histiocytes containing phagocyted erythrocytes of different degree of maturation and in various stages of destruction. They believe that this phenomenon is not continuous, but occurs according to a cycle, which shows, after an initial activity, a tendency to become quiescent or to stop altogether.

The erythrophagocytosis in the bone marrow and in other districts of the reticuloendothelial system other than the spleen (liver, lymph nodes) observed by different authors would explain, at least partially, the negative results of the splenectomy in Cooley's anemia.

The work is completed by the presentation of several anatomicopathological reports gathered from the world medical literature and by a rich and up-to-date bibliography.

U. Stefano.

Ecology of Health. The New York Academy of Medicine Institute on Public Health, 1947. E. H. L. Corwin, Ph.D., Editor, New York, 1949, Commonwealth Fund, 196 pages. Price $2.50.

A volume containing summaries of the discussions at the Institute of Public Health held as a part of the Academy Centennial Celebration in 1947. The volume differs from the usual "transactions" in that the papers and discussions of each of the panels have been thoroughly and carefully edited and presented in the form of a summary. It is an innovation that might well be followed in reporting by other institutes and panels, as it makes a most readable volume. Such a method calls for much work on the part of those responsible for the editing, but, as this volume shows, the effort is worth while. Panels with authoritative leaders and speakers were held on the following subjects: Genetics and Public Health; Animals and Insect Reservoirs of Disease; Climate, Geography, and Disease; Realities in Preventive Psychiatry; Trends in Development of State and Local Health Service; Professional and Lay Education in Support of Public Health; and Government and Public Health. The summaries of the various panels comprise over two-thirds of the volume and to these have been added three of the addresses which are published in full. It is difficult to discuss the panels in a book review, as each is presented in the form of a critically edited summary. They were all of interest to the reviewer, but the panel on "Animal and Insect Reservoirs of Disease" in particular can be singled out as opening a vista of the remarkable research that is taking place throughout the world in this field and of which the average physician and teacher has limited knowledge. The paper and print are excellent and the volume adds one more to the excellent series of medical contributions which have come out of the Centennial Celebration of the New York Academy of Medicine.

For the New Mother. Mildred V. Hardcastle, R.N., Philadelphia, 1948, The John C. Winston Company, 163 pages. Price $2.00.

This is another book for mothers on how to care for the baby during its first year of life. It is about average quality with the hundred-odd books covering the same field.

Editor's Column

MODEL MEDICAL REPORTING

A RECENT volume* reporting the papers and discussions at an Institute of Public Health of the Academy of Medicine in New York might well serve as a model for those who have the responsibility for reporting and publishing the proceedings of conferences, institute panel discussions, and the like. Every medical library has its shelves loaded with volumes of transactions and proceedings which give in detail (and usually in fine type) the papers and discussions which took place at the meeting. It makes, as a rule, for tiresome and dull reading. Frequently, important points and discussions are buried in a mass of trivialism.

In this volume a different method has been followed. At the Institute certain basic aspects of public health were considered and each is reported as a chapter. First the names of the half dozen or more authoritative speakers who took part in the discussion of the particular subject are given. This is followed by a carefully prepared report giving the quintessence of the discussions without reference to the individual contribution or discussants. The result is an interesting, readable essay, printed in type that can be read without eyestrain, which gives in relatively few words what was said at the discussion that was of importance.

It undoubtedly was not an easy task to summarize the discussions in this way, but the task of editing was well worth while judging from the impression made on this editor and the complimentary remarks he has heard by others who have read the book.

Incidentally, we are certain that many of our readers would find some of the discussions of interest and value. The discussion of "Genetics and the Public Health," for example, approaches the subject from a different viewpoint than we are accustomed to think of genetics. The discussion of "Animal and Insect Reservoirs of Disease" is one of the best in the book. We wonder how many physicians would come near the correct answer if asked the number of human diseases in which animals or insects are involved in the transmission. The information as to the number was so startling to the editor that he posed the above question to a number of medical school teachers. The answers were usually about 50 per cent wrong.

B. S. V.

*The Ecology of Health, The New York Academy of Medicine, Institute on Public Health, 1947, published by the Commonwealth Fund, New York, 1949.

CONTENTS FOR FEBRUARY, 1950

Original Communications

The Effect of Inherited Antibodies on the Active Immunization of Infants. Louis Greenberg, M.Sc., Ph.D., Ottawa, Ont., and Donald S. Fleming, M.D., D.P.H., Montreal, Que. ---- 143

Health and Growth of Aleut Children. Edwin Wilde, M.D., St. Paul Island, Alaska ---- 149

The Use of Phenurone in the Treatment of Epilepsy. Samuel Livingston, M.D., and Laslo Kajdi, M.D., Baltimore, Md. ---- 159

Tonic-Neck-Reflex and Symmetro-Tonic Behavior: Developmental and Clinical Aspects. Arnold Gesell, M.D., and Louise B. Ames, Ph.D., New Haven, Conn. ---- 165

Blood Sugar Values in Premature Infants, Mildred A. Norval, M.D., Rochester, Minn. ---- 177

Pre-Eruptive Neurological Complications of the Common Contagious Diseases—Rubella, Rubeola, Roseola, and Varicella. Pope B. Holliday, Jr., M.D., Nashville, Tenn. ---- 185

Urinary Lysozyme: III. Lysozymuria in Children with the Nephrotic Syndrome. Armine T. Wilson, M.D., and William P. Hadley, M.D., Wilmington, Del. ---- 199

The Incidence of Congenital Impatency of the Nasolacrimal Duct. Edwin L. Kendig, Jr., M.D., and DuPont Guerry III, M.D., Richmond, Va. ---- 212

Thrombosis of the Renal Vein in Infants. Charles Q. McClelland, M.D., and James P. Hughes, M.D., Cleveland, Ohio ---- 214

A Table Unit for Fluoroscopic Examination of Infants. Martin M. Maliner, M.D., Brooklyn, N. Y. ---- 228

Case Reports

Congestive Heart Failure in Utero. G. E. Rader, M.D., and Raymond D. Goodman, M.D., Los Angeles, Calif. ---- 230

Friedländer's Pneumonia with Multiple Lung Abscesses: Recovery Following the Use of Streptomycin and Aureomycin. Seymour Gruber, M.D., Richard D. Turin, M.D., S. David Sternberg, M.D., and Henry Rascoff, M.D., Brooklyn, N. Y. ---- 237

Potassium Bromate Poisoning. Harold F. Robertson, B.S., M.D., F.A.C.P., M. William Flothow, Jr., B.S., M.D., and Martin D. Kissen, A.B., M.D., Philadelphia, Pa. ---- 241

Juvenile Thyrotoxicosis Treated with Propyl Thiouracil and Two Subtotal Thyroidectomies. Louis D. Altman, M.D., Greensburg, Pa.--- 244

Clinical Conference

Conference at the Children's Hospital of Michigan. Dr. Paul V. Woolley, Jr., Pediatrician-in-Chief

1. Idiopathic Dilatation of the Common Bile Duct (Choledochal Cyst) 247
2. Obstruction of the Common Duct Due to Fibrous Tumor of the Pancreas ---- 251
3. Acute Hypertension, Probably Secondary to Infarctions Within a Congenitally Hypoplastic Kidney ---- 254
4. Polycystic Disease of the Kidneys ---- 259

Psychologic Aspects of Pediatrics

Psychic Trauma of Operations. Harry Bakwin, M.D., New York, N. Y. 262

Comments on Current Literature

Prophylaxis and Early Treatment of Infections in the Newborn Infant. Russell J. Blattner, M.D., Houston, Texas ---- 265

News and Notes

News and Notes ---- 267

Book Reviews

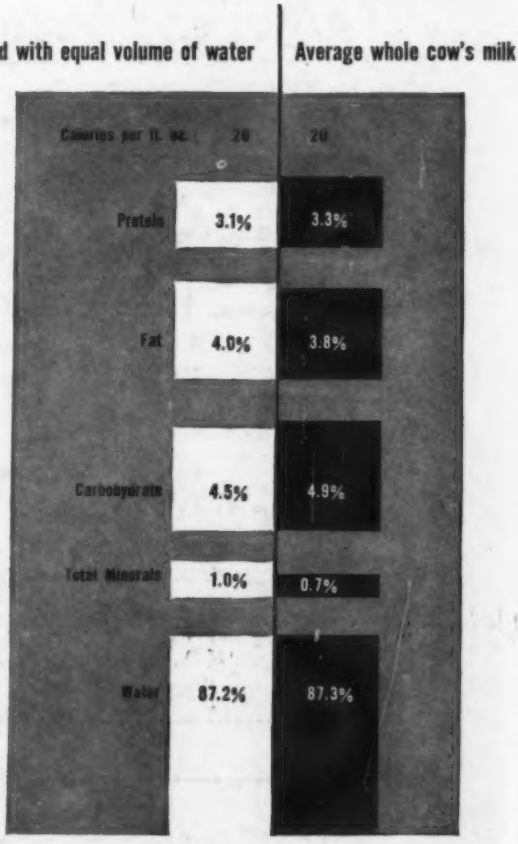
Book Reviews ---- 269

Editor's Column

Model Medical Reporting ---- 270

Not just milk replacement but casein replacement...

Casein—and also lactalbumin—are frequently the cause of hypersensitiveness to cow's milk. This hypersensitiveness can be manifested by gastrointestinal upsets followed in time by eczema of a mild or acute nature. In such cases cow's milk of all types must be eliminated from the diet. Mull-Soy is a near equivalent for milk to be used in these cases.



A scientifically sound formula for avoidance of casein allergy

Stable—vacuum packed

High in unsaturated fatty acids essential for growth

Pleasant-tasting

A homogenized liquid, not a powder or a hydrolysate

For hypoallergenic diet in infants or adults look to

MULL-SOY®

The Borden Company
Prescription Products Division
350 Madison Avenue, New York 17

At drugstores in 15½ oz. tins.